STATISTICAL ANALYSIS PLAN No DGD-55-003

THE NSsaFe STUDY

Observational Study on the incidence of NSF in renal impaired patients following DOTAREM® administration

SPONSOR GUERBET B.P. 57400 95943 ROISSY CHARLES DE GAULLE CEDEX - FRANCE Tel.: 33-1-45-91-5000 Fax: 33-1-45-91-5199	**STATISTICAL ANALYSIS PLAN APPROVAL**
BIOSTATISTICIAN Florence Praud Tel. 33-1-85-65-7735 e-mail : fpraud@inferential.fr	**Date and Visa**
BIOSTATISTICIAN Benoit PIEDNOIR Tel. 33-1-45-91-4642 e-mail : benoit.piednoir @guerbet-group.com	**Date and Visa**

HISTORY FORM

Version	Date	Statistician	Reason for change
1.0	12 october 2017	Benoit PIEDNOIR	Initial Version
2.0	26 february 2018	Florence PRAUD	Implementation of comments on 1.0

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
BMI	Body Mass Index
GBCA	Gadolinium based Contrast Agent
DRM	Data Review Meeting
eGFR	Estimated Glomerular Filtration Rate
MedDRA	Medical Dictionary For Regulatory Activities
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NSF	Nephrogenic Systemic Fibrosis
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

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1. SUMMARY OF THE STUDY PROTOCOL

This document presents the statistical analysis plan (SAP) for Guerbet, Protocol No. DGD-55-003: "**Observational study on the incidence of NSF in renal impaired patients following DOTAREM® administration**".

This analysis plan is based on the final protocol Version 1.0 dated November 08, 2010 + protocol amendment 1 dated July 24, 2012.

1.1. Study objectives

The primary objective of this study is to prospectively estimate the incidence of NSF in patients with moderate to severe renal impairment after administration of DOTAREM®. Patients will be followed during a two-year period after administration of DOTAREM®, to assess if signs or symptoms suggestive of NSF have appeared.

The secondary objectives of the study are:

- to collect a large number of data concerning the general safety profile of DOTAREM® during patient inclusion and MR examination,
- to collect information regarding MRI indication,
- to collect conditions of use/administration of the product in this specific population of patients,
- to collect efficacy data (image and diagnostic quality).

1.2. Study design

DGD-55-003 is a prospective multinational, multicenter, observational Post-Marketing Study (PMS) including longitudinal safety follow-ups. The number of sites and patients will vary from one country to another.
Patients included in the study should have moderate (eGFR of 30-59 ml/min/1.73 m^2) to severe (eGFR<30 ml/min/1.73 m^2) and end stage (eGFR<15 ml/min/1.73 m^2) renal impairment or dialysis and should be scheduled for a contrast-enhanced MRI with DOTAREM®.

After a patient has satisfied all eligibility requirements, he will undergo a MRI examination with a DOTAREM® administration. All patients will be followed up during 2 years after DOTAREM® administration to collect data on any suspected NSF or NSF related symptoms.

The images will be assessed on-site by the same investigator at each participating hospital.

Safety assessments will include adverse events that occurred during the MRI examination or during the time of usual follow-up post DOTAREM® administration.

1.3. Study contrast media

DOTAREM® (gadoterate meglumine)

2. EVALUATION CRITERIA

2.1. Demographic and other baseline characteristics

Demographic variables collected for this study are:

- Age in years for patient more than 2 years old and age in months otherwise,
- height,
- weight,
- sex.

Baseline characteristics collected for this study are:

- Magnetic field,
- Current renal status according to the investigator,
- Most recent serum creatinine before inclusion (in mg/L or mg/dL or µmol/L),
- Estimated creatinine clearance for children less than 2 years old and eGFR otherwise,
- Pre-existing risk factors and medical history,
- Previous examinations with GBCA,
- Concomitant treatment and recent surgery (<2 years),
- Indication of MRI examination,
- Premedication.

2.2. Efficacy criteria

The primary objective of the study is related to the NSF prevalence and therefore the primary criterion is not an efficacy criterion.
Efficacy variables are derived from the investigator evaluations of the imaging examination. Images will be rated regarding the following items:

- Image quality
- Diagnostic quality

2.3. Safety criteria

Safety variables collected for this study are:

- Modalities of DOTAREM® administration
  - Volume injected,
  - Type of injection,
  - Number of injections,
  - Nature of package
- From DOTAREM® administration until end of usual follow up in the MR unit
  - Adverse events,
  - Serious adverse events,
  - Adverse events requiring the administration of a concomitant drug,
  - Adverse events according to intensity and outcome,
  - Adverse events related to contrast media injection.
- During the follow-up period

- Suspicion of NSF and final diagnosis of NSF,
- Medical events,
- Serum creatinine measurements.

2.4. Other criteria

None

3. STATISTICAL METHODS

3.1. General considerations

At the end of the study, after the database lock, the statistical analysis will be performed by GUERBET Biostatistic team 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. Summary tabulated results will be provided by assessment time if relevant or they will be replaced by the corresponding individual data listings if too few patients are concerned.

Tabulations of quantitative parameters will include the following summary statistics: Number of Patients / Mean / Standard Deviation / Minimum / Median / Maximum. If for a given parameter, the raw value has been collected with x decimal places, the mean, median and standard deviation 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 (%). 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 recorded (non missing) data.

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

No statistical tests will be performed in this study. All statistics will be only descriptive.

SAS® Version: 9.4 will be used for all descriptive summaries.

3.2. Null and alternative hypothesis

None as no statistical test will be performed in this study.

3.3. Determination of sample size

This study aims at accurately estimating the incidence of the NSF in renal impaired patients, in case such an event is observed after injection of DOTAREM®. Assuming that when exposed to GBCA, the frequency of NSF is ranging from 0% to 4% in this population (maximum frequency being observed with linear GBCA), with a sample size of 1000 patients, a two-sided 95% exact confidence interval for a single proportion will allow to estimate with an adequate accuracy the frequency of this event according to the following table:

Observed cases	N	Observed frequency	Exact 95% IC
0	1000	0.0%	0.00% - 0.37%
1	1000	0.1%	0.00% - 0.56%
2	1000	0.2%	0.02% - 0.72%
5	1000	0.5%	0.16% - 1.16%
10	1000	1.0%	0.48% - 1.83%
15	1000	1.5%	0.84% - 2.46%
20	1000	2.0%	1.23% - 3.07%
30	1000	3.0%	2.03% - 4.26%

The sample size of 1000 patients was not reached before the end of the enrolment period (see section 4)

3.4. Adjustment for covariates

Not applicable

3.5. Handling of dropouts or missing data

If the start date of an adverse event is missing, then the adverse event occurs after the DOTAREM® injection.

No replacement of missing data is planned in this study.

3.6. Interim analyses and data monitoring

Not applicable

3.7. Multicentre studies

Number of patients included in each centre will be presented but no demographic parameters, baseline characteristics, efficacy or safety criteria will be presented by centre.

3.8. Multiple comparisons/Multiplicity

Not applicable

3.9. Use of an “efficacy subset” of patients

Efficacy results will be presented using the set of patients having an available diagnostic assessment.

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

The protocol was amended on one occurrence globally and twice in Turkey and twice in the United State of America (see protocol amendments for a full list of changes).

The global amendment has introduced following changes:

- The minimum number of patients with severe renal impairment was changed from 50% to 40% but this does not change the planned analysis as no analysis is foreseen considering the renal impairment status.
- The period of recruitment was extended. Initially 1000 patients were supposed to be included in the study with a minimum of 50% of patients with severe renal impairment. Despite the extension of the recruitment period, the sample size of 1000 patients was not reached by the end of the recruitment period. Thanks to better understanding of causality and risk factors conducting to NSF occurrence, safety and educational measures starting from 2012, the rate of NSF appears to be less than 1%, and the study was no longer powered to assess the NSF rate. For this reason and taken into account that the NSF was not a safety priority for the competent authorities anymore due to the low incidence, the recruitment was stopped in March 2015.
- Patients who had received DOTAREM® within 12 months prior to inclusion were included in the study.

The methodology of statistical testing is described in the protocol although no comparison is possible. No statistical tests will be presented in the report.

5. STATISTICAL AND ANALYTICAL PLANS

5.1. Disposition of patients

Patient disposition will be based on all included patients (that is to say patients included in the study by having a questionnaire partly or fully filled in) and will display patients prematurely withdrawn of the study and reasons why patients were prematurely withdrawn.

Frequency of patients by centre within country and frequency of patients by visits will be tabulated. Amongst patients indicated as having undergone the follow-up, some were indicated as being prematurely withdrawn from the study. These patients had either no results collected at this visit or only one result (no suspicion of NSF), therefore it has been decided that the reliable data is the withdrawal form and so these patients were eventually considered as having not undergone the follow-up 3 visit.

Centre characteristics and radiological activities of centres will be tabulated.

A listing showing disposition of patients and a listing showing centre characteristics and radiological activities of centres will be provided in CSR appendix 16.2.1.

5.2. Data Sets Analysed and protocol deviations

Data sets analysed
There will be three patient populations defined for this study: all-included population (AIP), safety population (SP) and efficacy population (EP).

The all-included population (AIP) will include all patients who have a questionnaire partly or fully filled in. This population will be used for the description of disposition of patients, protocol deviations and demographic data.

The safety population (SP) will include all patients receiving at least one injection of contrast media regardless of the quantity. This population will be used to evaluate the NSF occurrence, to describe administration modalities, for analysis of adverse events, laboratory data, other safety observations, medical events and concomitant medications presentation. Furthermore, demographic data and medical history will be presented using this population as well.

The efficacy population (EP) will include all patients who have an available imaging assessment.

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

Analysed populations

Analysed Populations	AIP	SP	EP
Population characteristics	✓(only Demographics)	✓	
Exposure		✓	
Efficacy assessment			✓
Safety assessment : Main criterion		✓	
Safety assessment : Secondary criteria (AE, laboratory data and other safety observation)		✓	
Concomitant medications		✓	

Frequency and percentages of patients in each population will be presented. A listing showing the distribution of each patient in the populations will also be provided in CSR appendix 16.2.3.

Protocol deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being. Protocol deviations are to be displayed in the Clinical Study Report (CSR) as a metric of the feasibility and reliability of the study.
The list of protocol deviations is defined in this document but protocol deviations can be added during the Data Review Meeting (DRM). Protocol deviations will be extensively sought from, clinical database and monitoring files (if monitoring was required as per local regulation).
As no efficacy or safety subset are defined, no deviation will lead to exclusion from this subset and therefore deviations will not be split in major and non major deviations.

The deviations are listed in the table below:

Category	Description
Inclusion/Non-inclusion criteria not met	Patient **not** scheduled for a contrast enhanced MRI with DOTAREM® or who will not be followed up for his/her renal impairment by one of the site study co-investigators
	Patient having mild renal impairment (eGFR 60-89 mL/min/1.73 m^2) or normal renal function (eGFR>90 mL/min/1.73 m^2)
	Patient has received a GBCA other than DOTAREM® within the past 12 months prior to inclusion in this study
	Patient has experienced a previous hypersensitivity reaction to GBCA
Non respect of study schedule and procedures	Patient is not injected
	Follow-up 1 visit is not performed

	Follow-up 2 visit is not performed
	Follow-up 3 visit is not performed
	Follow-up 1 visit is not done between 3 and 12 months after the study drug administration
	Follow-up 2 visit is not done between 13 and 21 months after the study drug administration
	Follow-up 1 visit is not done between 22 and 27 months after the study drug administration
	The interval of at least 3 months was not respected between two follow-up visits.

No deviation will lead to exclusion from analyses in this safety study.

5.3. Measurements of study drug compliance

None

5.4. Demographic and Other Baseline Characteristics

All demographic variables and other baseline characteristics will be presented using the SP. Demographics variables will be presented using the AIP as well.

Demography
Summary statistics for quantitative variable will be calculated for age, body weight, height and BMI. Frequency and percentages will be calculated for gender.

BMI will be derived for each collection of body weight using the formula: $BMI = \frac{BodyWeight\_(Kg)}{Height\_(m)^2}$

Magnetic Field
Summary statistics for qualitative variable will be presented for magnetic field (in tesla).

Current renal status
Summary statistics for quantitative variable will be calculated for serum creatinine, estimated creatinine clearance and eGFR. Frequency and percentages will be calculated for current renal status.
Serum creatinine will be presented in µmol/L. Therefore, conversion will apply for measurement in mg/L and mg/dL using the following conversion factors [1]:
From mg/dL to µmol/L: multiply by 88.4
From mg/L to µmol/L: multiply by 8.84
Should be noted that an aberrant result of serum creatinine was entered in the database for one patient (1.36 µmol/L). As it was impossible to correct this discrepancy in the database, it was decided not to present it in the statistical results of the clinical study report.

The estimated creatinine clearance (mL/min) will be calculated using the Schwartz formula for children less than 2 years old. The eGFR (mL/min/1.73 m²) will be calculated using the MDRD formula otherwise. They will be presented independently.

Risk factors
Frequency and percentages will be calculated for each risk factor. Specification for other cardiovascular disease, nervous system disorders, other treatments at risk and dose of Erythropoietin will be only listed.

Previous examination with GBCA
Number of patients with at least one previous examination with GBCA will be displayed globally and by classified name of product. Name of product will be classified as the following:

- If the words "Gadovist" or "Gadavist" appear in the product name then class=" Gadobutrol"
- If the word "Dotarem" appears in the product name then class= " Gadoterate meglumine"
- If the word "Primovist" or "Gd-EOB-DTPA" or "Gd EOB" appear in the product name then class= "Gadotexate disodium"
- If the words "Magnevist" or "Gadopentetate" appear in the product name then class= " Gadopentetate dimeglumine"
- If the word "Multihance" appears in the product name then class= "Gadobenic acid meglumine"
- If the word "Omniscan" appears in the product name then class= "Gadodiamide"
- If the word "Optimark" appears in the product name then class="Gadoversetamide"
- If the words "No contrast" or "without contrast" or "NA" or "Non-contrast brain MRI" appear in the product name then class = "Without Contrast"
- If the words "Unknown" or "MD" or "UN" or nothing appear in the product name then class = "Missing"
- Otherwise then class="Other"

Recent surgeries
Surgeries done less than two years before the MRI examination with DOTAREM® will be only listed. Number of patients with at least one surgery will be tabulated.

Concomitant treatments
Concomitant treatments at the time of the MRI examination with DOTAREM® will only be listed. Number of patients with at least one concomitant medication will be tabulated.

Indication of MRI examination
Indication of MRI examination will be tabulated by main classification (Central nervous system, whole body, musculoskeletal system, angiography and other) and sub classification.
Some indications for MRI categorized as "Other" should be classified in pre-defined categories according to the following algorithm:
If the wording contains "angio" or "anjio" then classify to Angiography system and according to the following for the sub classification:

If the wording is:	Specified Organ
"kidney"or "kidneys" or "renal" or contains one of these	2=Renal

"iliac" or contains "iliac"	3=Aorto iliac
"calf"	4=Calf
"Otherwise"	5=Other

Otherwise classify to whole body system and according to the following. for the sub classification:

If the wording is:	Specified Organ
"liver" or contains "lilver"	1=Liver
"kidney"or "kidneys" or "renal" or contains one of these	2=Kidney
"pancreas"	3=Pancreas
"pelvis" or contains "pelvic" or contains "pelvin"	4=Pelvis
"lung"	5=Lung
"heart" or "cardiac"or "cardio"	6=Heart
"breast"	7=Breast

Premedication
Patients having received at least one premedication will be presented. Premedication received will be only listed.

Listings of all demographic parameters and baseline characteristics will be presented in CSR Appendix 16.2.4.

5.5. Efficacy evaluation

All efficacy analyses will be conducted using the EP.

Image quality
Frequency of images with very poor, poor, fair, good and very good quality will be presented.

Diagnostic quality
Diagnosis assessment (Yes/No) and reason for impossible diagnosis will be tabulated. Diagnosis when available will be listed.

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

5.6. Safety Evaluation

All safety analyses will be conducted using the SP.

5.6.1. Extent of Exposure

Extent of exposure will present the DOTAREM® administration: total volume injected, type of injection, number of injections (1 or 2), nature of package, and volume of vial and pre-filled syringe used. Total dose injected (mL/kg), calculated by dividing the total volume of DOTAREM® administered by the body weight will be presented as well.
Summary statistics for quantitative variable will be calculated for total volume injected and total dose injected. Frequency and percentages will be calculated for other criteria.

Listing of exposure will be presented in CSR appendix 16.2.5.

5.6.2. Primary safety endpoint: NSF

The number and percentage of patients with any suspicion of NSF will be presented.

For patients having any suspicion of NSF, the reasons of the suspicion will be tabulated

Among patient having any suspicion of NSF, the number and percentage of patients with a confirmatory biopsy or not (and the reason if not) will be presented.

Among patients having a confirmatory biopsy, the number and percentage of patients with a final diagnosis of NSF or not (and the reason if not) will be presented.

Listing of NSF suspicion and diagnosis will be presented in CSR appendix 16.2.9.1

5.6.3. Adverse Events

Adverse events (AEs) will be coded in system organ classes and preferred terms using MedDRA dictionary v16.0.

Adverse events occurring or worsening after the "Treatment start date" (Date of MRI examination with DOTAREM®) will be considered as **treatment-emergent** adverse events (TEAEs).

An adverse event will be considered **related to** DOTAREM®, if the relationship to the study drug is doubtful, possible, not assessable or missing.

All AEs will be summarized in an incidence table and a specific table will focus on incidence of TEAEs.

Incidence tables will present the number and percent of patients reporting TEAEs, the number and percent of patients reporting serious adverse events (SAEs) and the number and percent of patients reporting related AEs by system organ class and preferred term.

Adverse event listings will be presented in CSR appendix 16.2.7.

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

All deaths and all SAEs experienced during the study will be separately listed sorted by patient number, presenting: , emergence, diagnosis or nature, system organ class (SOC), preferred term (PT), start date, the intensity, the relationship to study drug, the outcome, the action taken and the seriousness criteria.

5.6.5. Clinical laboratory evaluation

Serum creatinine collected during the follow-up period will be tabulated as quantitative parameter by visit in raw data and change from baseline. If during the follow-up visits, the date of last renal function assessment is replicated then only the first measurement will be taken into account.
Serum creatinine will be presented in µmol/L. Therefore, conversion will apply for measurement in mg/L and mg/dL using the following conversion factors [1]:
From mg/dL to µmol/L: multiply by 88.4
From mg/L to µmol/L: multiply by 8.84

Listing of clinical laboratory evaluation will be presented in CSR appendix 16.2.8.

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

Medical events will be coded in body systems and preferred terms using MedDRA dictionary v16.0.

Medical Event overview
Number and percentage of patient having undergone medical events will be tabulated by follow-up visit

MRI examination
Number of patients with MRI examination will be displayed by follow-up visit and by name of product. Name of product will be coded using WHO DD 2015 version and will be tabulated according to ATC code.

Medical Event by SOC and PT
Medical events will be displayed by follow-up visit and by SOC and PT.

Listing of medical events will be presented in CSR appendix 16.2.9.

6. LIST OF TABLES, FIGURES AND LISTINGS

6.1. Clinical study report in-text tables, figures and listings

6.2. Contents of clinical study report section 14

6.2.1. Demographic Data Summary and Figures (Section 14.1 of ICH report)

6.2.1.1 Disposition of Patients

6.2.1.2 Protocol Deviations

6.2.1.3 Data Set Analysed

6.2.1.4 Demographics and Baseline Characteristics

6.2.2. Efficacy Data Summary Figures and Tables
(Section 14.2 of ICH report)

6.2.2.1 Primary Efficacy Variables
(Section 14.2.1 of ICH report)

Not applicable.

6.2.2.2 Secondary Efficacy Variables

Table 14.2.2.1	Overall Quality of Images - Efficacy Population
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6.2.3. Safety Data Summary Figures and Tables
(Section 14.3 of ICH report)

6.2.3.1 Extent of Exposure

Table 14.3.1.1	DOTAREM® Administration at Inclusion Visit - Safety Population

6.2.3.2 NSF suspicion and diagnoses

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Table 14.3.2.2	Confirmatory Biopsy and Final Diagnosis - Safety Population - Patient with Suspicion of NSF

6.2.3.3 Displays of Adverse Events

Table 14.3.3.1	Overall Safety Summary - Safety Population
Table 14.3.3.2	Treatment Emergent Adverse Events - Overall Summary - Safety Population
Table 14.3.3.3	Pre-injection Adverse Events by Primary System Organ Class and Preferred Term - Safety Population
Table 14.3.3.4	Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term - Safety Population
Table 14.3.3.5	Serious Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term - Safety Population
Table 14.3.3.6	Treatment Emergent Adverse Events with Relationship to DOTAREM® by Primary System Organ Class and Preferred Term - Safety Population

6.2.3.4 Listings of Deaths, Other Serious and Significant Adverse Events

Table 14.3.3.7	Listing of Deaths - Safety Population
Table 14.3.3.8	Listing of Serious Adverse Events - Safety Population

6.2.3.5 Narratives of Deaths, Other Serious and Significant Adverse Events

Not applicable.

6.2.3.6 Display of Clinical Laboratory Data

Table 14.3.4.1	Renal Status during Follow-up Period - Safety Population

6.2.3.7 Vital Signs, Physical Findings and Other Observations Related to Safety

Table 14.3.5.1	Medical Events except MRI Examination during Follow-up Period - Safety Population
Table 14.3.5.2	Contrast Media for MRI Examination during Follow-up Period - Safety Population
Table 14.3.5.3	Medical Events except MRI Examination during Follow-up Period by Primary System Organ Class and Preferred Term - Safety Population

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6.3.1. Disposition of Patients

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Listing 16.2.1.1	Visit Dates - All Included Population
Listing 16.2.1.2	Premature Withdrawal
Listing 16.2.1.3	Centre Characteristics and Radiological Activities

6.3.2. Protocol Deviations

(Section 16.2.2 of ICH report)

Listing 16.2.2.1	Protocol Deviations - All Included Population

6.3.3. Patients Excluded from Efficacy Analysis

(Section 16.2.3 of ICH report)

Listing 16.2.3.1	Analysis Data Populations - All Included Population

6.3.4. Demographic Data and Baseline Characteristics

(Section 16.2.4 of ICH report)

Listing 16.2.4.1	Demographics - All Included Population
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Listing 16.2.4.4	Risk Factors and Medical History - All Included Population
Listing 16.2.4.5	Previous Examinations with GBCA - All Included Population

Listing 16.2.4.6	Recent Surgery - All Included Population
Listing 16.2.4.7	Concomitant Medications - All Included Population
Listing 16.2.4.8	Indication of Current MRI Examination - All Included Population
Listing 16.2.4.9	Premedication - All Included Population

6.3.5. Compliance and/or Drug Concentration Data

(Section 16.2.5 of ICH report)

Listing 16.2.5.1	DOTAREM® Administration - All Included Population

6.3.6. Individual Efficacy Response Data

(Section 16.2.6 of ICH report)

Listing 16.2.6.1	Overall Quality of Images and Diagnostic Quality - All Included Population

6.3.7. Adverse Event Listings

(Section 16.2.7 of ICH report)

Listing 16.2.7.1	Adverse Events - All Included Population

6.3.8. Listing of Individual Laboratory Measurements

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Listing 16.2.8.1	Renal Status during Follow-up Period - All Included Population

6.3.9. Vital signs, Physical Findings and Other Observations Related to Safety

(Section 16.2.9 of ICH report)

Listing 16.2.9.1	Nephrogenic Systemic Fibrosis Suspicion/Diagnosis - All Included Population
Listing 16.2.9.2	Medical Events during Follow-up Period except MRI Examination - All Included Population
Listing 16.2.9.3	MRI examination during Follow-up Period - All Included Population

7. SHELLS FOR TABLES, FIGURES AND LISTINGS

All outputs will be produced using SAS® version 9.2.

The listings will include all patients and will be ordered by site and patient.

7.1. Clinical study report in-text tables, figures and listings

7.2. Contents of clinical study report section 14

Table 14.1.1.1 Patient Overall Disposition - All Included Population

		Total (N=XXX)
Number of Patients not Prematurely Withdrawn		xxx (xx.x%)
Number of Patients Prematurely Withdrawn		xxx (xx.x%)
Reason of Withdrawal	Retraction of Patient Consent	xxx (xx.x%)
	Adverse Event	xxx (xx.x%)
	Patient Lost to Follow-up	xxx (xx.x%)
	Technical Incident	xxx (xx.x%)
	Death	xxx (xx.x%)
	Medical Decision	xxx (xx.x%)
	Other	xxx (xx.x%)

%: (n row / N included) * 100.
Source: Listing 16.2.1.2.

Table 14.1.1.2 Disposition by Visit - All Included Population

	General Questionnaire (N=XXX)	**Follow-up 1** (N=XXX)	**Follow-up 2** (N=XXX)	**Follow-up 3** (N=XXX)	**At Least One Follow-up Visit**
Number of Patients	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

%: (n row / N included) * 100.
Source: Listing 16.2.1.1.

Table 14.1.1.3 Disposition by Site - All Included Population

		Total (N=XXX)
Argentina	Site 29	xxx (xx.x%)
	Site 30	xxx (xx.x%)
	Site 31	xxx (xx.x%)
Belgium	Site 1	xxx (xx.x%)

		Total (N=XXX)
	Site 2	xxx (xx.x%)
	Site 28	xxx (xx.x%)
Brazil	Site 3	xxx (xx.x%)
Columbia	Site 32	xxx (xx.x%)
	Site 33	xxx (xx.x%)
	Site 34	xxx (xx.x%)
France	Site 6	xxx (xx.x%)
	Site 26	xxx (xx.x%)
Germany	Site 8	xxx (xx.x%)
	Site 27	xxx (xx.x%)
India	Site 10	xxx (xx.x%)
Italy	Site 12	xxx (xx.x%)
	Site 13	xxx (xx.x%)
	Site 14	xxx (xx.x%)
Korea	Site 15	xxx (xx.x%)
	Site 16	xxx (xx.x%)
	Site 17	xxx (xx.x%)
	Site 18	xxx (xx.x%)
Spain	Site 19	xxx (xx.x%)
	Site 20	xxx (xx.x%)
	Site 35	xxx (xx.x%)
Turkey	Site 23	xxx (xx.x%)
	Site 37	xxx (xx.x%)
United Kingdom	Site 24	xxx (xx.x%)
	Site 25	xxx (xx.x%)
Uruguay	Site 36	xxx (xx.x%)
United States of America	Site 38	xxx (xx.x%)
	Site 39	xxx (xx.x%)

		Total (N=XXX)
	Site 40	xxx (xx.x%)
	Site 41	xxx (xx.x%)

%: (n row / N included) * 100.
Source: Listing 16.2.1.1.

Table 14.1.1.4 Centre Characteristics and Radiological Activities - All Centres

		Total (N=XX)
Type of Centre	n	xx
	Private	xx (xx.x%)
	Public	xx (xx.x%)
	Other	xx (xx.x%)
	Missing *(if applicable)*	xx
Radiological Fields or Specialities*	Neurology	xx (xx.x%)
	Cardiology	xx (xx.x%)
	Peripheral Vascular	xx (xx.x%)
	Musculoskeletal	xx (xx.x%)
	Oncology	xx (xx.x%)
	Other	xx (xx.x%)
Number of MR Equipment	n	xx
	1	xx (xx.x%)
	2	xx (xx.x%)
	3	xx (xx.x%)
	4	xx (xx.x%)
	5	xx (xx.x%)
	Missing *(if applicable)*	xx
Number of MR Examinations/Week	n	xxx
	Mean (SD)	xx.x (xx.x)
	Median	xx
	Min ; Max	xx ; xx
	Missing *(if applicable)*	xx
Usual Practice in MR Units		
Allergic History Assessment	n	xx
	Yes	xx (xx.x%)
	No	xx (xx.x%)
	Missing *(if applicable)*	xx

		Total (N=XX)
Creatinine Level Assessment	n	xx
	Yes	xx (xx.x%)
	No	xx (xx.x%)
	Missing *(if applicable)*	xx
Other Assessment	n	xx
	Yes	xx (xx.x%)
	No	xx (xx.x%)
	Missing *(if applicable)*	xx
Patient Consent Form Signature	n	xx
	Yes	xx (xx.x%)
	No	xx (xx.x%)
	Missing *(if applicable)*	xx
Duration of Follow-up After MR Examination	n	xx
	< 30 min	xx (xx.x%)
	Between 30 min and 1 hour	xx (xx.x%)
	> 1 hour	xx (xx.x%)
	Missing *(if applicable)*	xx

MR: Magnetic Resonance.
%: (n row / n non missing) * 100, except for multiple answers %: (n row / N centre) * 100.
*As multiple radiological fields or specialities are possible, the sum of percentage could be greater than 100.
Source: Listing 16.2.1.3.

Table 14.1.1.5 Magnetic Fields of MR Equipments - All MR Equipments

		Total (N=XX)
Magnetic Fields	1.5	xx (xx.x%)
	3.0	xx (xx.x%)
	Missing *(if applicable)*	xx

MR: Magnetic Resonance.
%: (n row / N MR equipment) * 100.
Source: Listing 16.2.1.3.

Table 14.1.2.1 Protocol Deviations - All Included Population

	Total (N=XXX)
At Least One Protocol Deviation	xxx (xx.x%)
Protocol Deviation 1	xxx (xx.x%)
…	…
Protocol Deviation n	xxx (xx.x%)

%: (n row / N included) * 100.
Source: Listing 16.2.2.1.

Table 14.1.3.1 Analysis Data Populations - All Included Population

	Total (N=XXX)
Safety Population	xxx (xx.x%)
Efficacy Population	xxx (xx.x%)

%: (n row / N included) * 100.
Source: Listing 16.2.3.1.

Table 14.1.4.1.1 Demographic Characteristics - All Included Population

		Total (N=XXX)
Sex	n	xxx
	Male	xxx (xx.x%)
	Female	xxx (xx.x%)
	Missing *(if applicable)*	xx
Age (years) for Patients Older than Two Years Old	n	xxx
	Mean (SD)	xx.x (xx.x)
	Median	xx
	Min ; Max	xx ; xx
	Missing *(if applicable)*	xx
Age (month) for Patients Younger than Two Years Old	n	xxx
	Mean (SD)	xx.x (xx.x)
	Median	xx
	Min ; Max	xx ; xx
	Missing *(if applicable)*	xx
Weight (kg)	n	xxx
	Mean (SD)	xx.x (xx.x)
	Median	xx
	Min ; Max	xx ; xx
	Missing *(if applicable)*	xx
Height (cm)	n	xxx
	Mean (SD)	xx.x (xx.x)
	Median	xx

		Total (N=XXX)
	Min ; Max	xx ; xx
	Missing *(if applicable)*	xx
Body Mass Index (kg/m²)	n	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median	xx.x
	Min ; Max	xx.x ; xx.x
	Missing *(if applicable)*	xx
Body Mass Index by Class	n	xxx
	< 18.5 kg/m²	xxx (xx.x%)
	≥ 18.5 and < 25 kg/m²	xxx (xx.x%)
	≥ 25 and < 30 kg/m²	xxx (xx.x%)
	≥ 30 kg/m²	xxx (xx.x%)
	Missing *(if applicable)*	xx

SD: Standard Deviation.
%: (n row / n non missing) * 100.
Source: Listing 16.2.4.1.

Table 14.1.4.1.2 Demographic Characteristics – Safety Population

Same as table 14.1.4.1.2

Table 14.1.4.2 Magnetic Field - Safety Population

		Total (N=XXX)
Magnetic Field (Tesla)	n	xxx
	1.5	xxx (xx.x%)
	3	xxx (xx.x%)
	Missing *(if applicable)*	xx

%: (n row / n non missing) * 100.
Source: Listing 16.2.4.2.

Table 14.1.4.3 Current Renal Status - Safety Population

		Total (N=XXX)
Intensity of Impaired Renal Function	n	xxx
	Moderate	xxx (xx.x%)
	Severe	xxx (xx.x%)
	End Stage Renal Insufficiency or Dialysis	xxx (xx.x%)

		Total (N=XXX)
	Kidney Transplantation	xxx (xx.x%)
	Missing *(if applicable)*	xx
If End Stage Renal Insufficiency or Dialysis, Specify	n	xxx
	Hemodialysis	xxx (xx.x%)
	Peritoneal Dialysis	xxx (xx.x%)
	Missing *(if applicable)*	xx
Most Recent Serum Creatinine (µmol/L)	n	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median	xx.x
	Min ; Max	xx.x ; xx.x
	Missing *(if applicable)*	xx
Estimated Creatinine Clearance (mL/min) for Patients Younger than 2 Years Old		xxx (xx.x%)
If Yes, Estimated	n	xx
	Mean (SD)	xx.xx (xx.xx)
	Median	xx.x
	Min ; Max	xx.x ; xx.x
	Missing *(if applicable)*	xx
eGFR (mL/min/1.73 m^2) for Patients Older than 2 Years Old		xxx (xx.x%)
If Yes, eGFR	n	xx
	Mean (SD)	xx.xx (xx.xx)
	Median	xx.x
	Min ; Max	xx.x ; xx.x
	Missing *(if applicable)*	xx

eGFR: Estimated Glomerular Filtration Rate.
SD: Standard Deviation.
%: (n row / n non missing) * 100, except for Estimated Creatinine Clearance and eGFR variables %: (n row / N safety population) * 100.
Source: Listing 16.2.4.3.

Table 14.1.4.4 Pre-existing Risk Factor and Medical History - Safety Population

		Total (N=XXX)
Liver Disorder		xxx (xx.x%)
Allergies		xxx (xx.x%)
Previous Reaction to Contrast Agents		xxx (xx.x%)
	GBCA	xxx (xx.x%)
	Iodinated Contrast Agent	xxx (xx.x%)
Bronchial Asthma		xxx (xx.x%)
Hypertension		xxx (xx.x%)
Heart Insufficiency		xxx (xx.x%)
	NYHA Class I	xxx (xx.x%)
	NYHA Class II	xxx (xx.x%)
	NYHA Class III	xxx (xx.x%)
	NYHA Class IV	xxx (xx.x%)
Other Cardiovascular Disease		xxx (xx.x%)
Diabetes Mellitus		xxx (xx.x%)
	Type I	xxx (xx.x%)
	Type II	xxx (xx.x%)
Proteinuria		xxx (xx.x%)
Nervous System Disorders		xxx (xx.x%)
At Risk Treatments		xxx (xx.x%)
	Beta-Blockers	xxx (xx.x%)
	Interleukine2	xxx (xx.x%)
	Other	xxx (xx.x%)
Hypothyroidism		xxx (xx.x%)
History of Deep Venous Thrombosis		xxx (xx.x%)
Erythropoietin		xxx (xx.x%)
Acidosis		xxx (xx.x%)
Hyperphosphatemia		xxx (xx.x%)
Abnormal Ca^{++} Level		xxx (xx.x%)
High Serum Ferritin Level		xxx (xx.x%)

GBCA: Gadolinium based Contrast Agent ; NYHA: New York Heart Classification.
%: (n row / N safety population) * 100.
Source: Listing 16.2.4.4.

Table 14.1.4.5 Previous Examinations with GBCA - Safety Population

		Total (N=XXX)
Previous Examination	n	xxx
	Yes	xxx (xx.x%)
	No	xxx (xx.x%)

		Total (N=XXX)
	Missing *(if applicable)*	xx
If Yes*	Gadobutrol	xxx (xx.x%)
	Gadoterate Meglumine	xxx (xx.x%)
	…	…
	Without Contrast	xxx (xx.x%)
	Missing	xxx (xx.x%)

GBCA: Gadolinium based Contrast Agent.
%: (n row / n non missing) * 100, except for multiple answers %: (n row / n with previous examination) * 100.
*As multiple examinations with various GBCA are possible, the sum of percentage could be greater than 100.
Source: Listing 16.2.4.5.

Table 14.1.4.6 Recent Surgery - Safety Population

		Total (N=XXX)
At Least One Recent Surgery	n	xxx
	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	Missing (*if applicable*)	xx

%: (n row / n non missing) * 100.
Source: Listing 16.2.4.6.

Table 14.1.4.7 Concomitant Medications - Safety Population

		Total (N=XXX)
At Least One Concomitant Medication	n	xxx
	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	Missing (*if applicable*)	xx

%: (n row / n non missing) * 100.
Source: Listing 16.2.4.7.

Table 14.1.4.8 Indication of MRI Examination - Safety Population

		Total (N=XXX)
Central Nervous System		xxx (xx.x%)
	Head/Neck	xxx (xx.x%)
	Brain	xxx (xx.x%)
	Spinal Cord	xxx (xx.x%)
Whole Body		xxx (xx.x%)
	Liver	xxx (xx.x%)
	Kidney	xxx (xx.x%)

		Total (N=XXX)
	Pancreas	xxx (xx.x%)
	Pelvis	xxx (xx.x%)
Other Cardiovascular Disease		xxx (xx.x%)
	Lung	xxx (xx.x%)
	Heart	xxx (xx.x%)
	Breast	xxx (xx.x%)
Musculoskeletal System		xxx (xx.x%)
	Bones/Joints	xxx (xx.x%)
	Soft Tissue	xxx (xx.x%)
Angiography		xxx (xx.x%)
	Carotids	xxx (xx.x%)
	Renal	xxx (xx.x%)
	Aorto Iliac	xxx (xx.x%)
	Calf	xxx (xx.x%)
	Other	xxx (xx.x%)
Other		xxx (xx.x%)

MRI: Magnetic Resonance Imaging.
%: (n row / N safety population) * 100.
Source: Listing 16.2.4.8.

Table 14.1.4.9 Premedications - Safety Population

		Total (N=XXX)
At Least One Premedication	n	xxx
	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	Missing (*if applicable*)	xx

%: (n row / n non missing) * 100.
Source: Listing 16.2.4.9.

Table 14.2.2.1 Overall Quality of Images - Efficacy Population

		Total (N=XXX)
Image Quality	n	xxx
	Very Good	xxx (xx.x%)
	Good	xxx (xx.x%)
	Fair	xxx (xx.x%)
	Poor	xxx (xx.x%)
	Very Poor	xxx (xx.x%)
	Missing (*if applicable*)	xx

%: (n row / n non missing) * 100.

Source: Listing 16.2.6.1.

Table 14.2.2.2 Diagnostic Quality - Efficacy Population

		Total (N=XXX)
Diagnosis	n	xxx
	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	Missing (*if applicable*)	xx
If No, Reason*	Technical Problem	xxx (xx.x%)
	Anxious Patient	xxx (xx.x%)
	Other	xxx (xx.x%)

%: (n row / n non missing) * 100, except for multiple answers %: (n row / n with no diagnosis) * 100.
*As multiple reasons are possible, the sum of percentage could be greater than 100.
Source: Listing 16.2.6.1.

Table 14.3.1.1 DOTAREM® Administration at Inclusion Visit - Safety Population

		Total (N=XXX)
Total Volume Injected (mL)	n	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median	xx.x
	Min ; Max	xx.x ; xx.x
	Missing *(if applicable)*	xx
Total Dose Injected (mL/kg)	n	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median	xx.x
	Min ; Max	xx.x ; xx.x
	Missing *(if applicable)*	xx
Type of Injection	n	xxx
	Manual	xxx (xx.x%)
	Automatic	xxx (xx.x%)
	Missing *(if applicable)*	xx
Number of Injections	n	xxx
	1	xxx (xx.x%)
	2	xxx (xx.x%)
	Missing *(if applicable)*	xx
Nature of Package	n	xxx

		Total (N=XXX)
	Vial	xxx (xx.x%)
	Pre-Filed Syringe	xxx (xx.x%)
	Vial and Pre-Filed Syringe	xxx (xx.x%)
	Missing *(if applicable)*	xx
Volume of Vial (mL)	n	xxx
	5 mL	xxx (xx.x%)
	10 mL	xxx (xx.x%)
	15 mL	xxx (xx.x%)
	20 mL	xxx (xx.x%)
	60 mL	xxx (xx.x%)
	100 mL	xxx (xx.x%)
	Missing *(if applicable)*	xx
Volume of Pre-filled Syringe (mL)	n	xxx
	10 mL	xxx (xx.x%)
	15 mL	xxx (xx.x%)
	20 mL	xxx (xx.x%)
	Missing *(if applicable)*	xx

SD: Standard Deviation.
%: (n row / n non missing) * 100.
Source: Listing 16.2.5.1.

Table 14.3.2.1 Suspected NSF - Safety Population

		Total (N=XXX)
Suspicion of NSF	n	xxx
	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	Missing *(if applicable)*	xx
If Yes,		
Skin*	Burning and Itching	xxx (xx.x%)
	Darkened Patches	xxx (xx.x%)
	Painful Skin Swelling	xxx (xx.x%)
Eyes*	Yellow Raised Spots	xxx (xx.x%)
Bones, Joints and Muscles*	Joint Stiffness	xxx (xx.x%)
	Limited Range of Motion	xxx (xx.x%)

		Total (N=XXX)
	Deep Pain	xxx (xx.x%)
	Muscle Weakness	xxx (xx.x%)
	Calcification of the Soft Tissue	xxx (xx.x%)
Systemic Fibrosis*	Fibrosis	xxx (xx.x%)

NSF: Nephrogenic Systemic Fibrosis.
%: (n row / n non missing) * 100, except for multiple answers %: (n row / n with suspicion of NSF) * 100.
*As the suspicion of NSF can be based on multiple topics, the sum of percentage could be greater than 100.
Source: Listing 16.2.9.1.

Table 14.3.2.2 Confirmatory Biopsy and Final Diagnosis - Safety Population - Patient with Suspicion of NSF

		Total (N=XXX)
Confirmatory Biopsy	n	xxx
	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	Missing *(if applicable)*	xx
If Yes, Final Diagnosis of NSF	n	xxx
	Yes	xxx (xx.x%)
	No	xxx (xx.x%)
	Missing *(if applicable)*	xx

NSF: Nephrogenic Systemic Fibrosis.
%: (n row / n non missing) * 100, except for Final Diagnosis of NSF %: (n row / n with confirmatory biopsy) * 100.
Source: Listing 16.2.9.1.

Table 14.3.3.1 Overall Safety Summary - Safety Population

	Patients	**AEs**
At Least One Adverse Event (AE)	xxx (xx.x%)	xxx
Distribution of AE		
- 0	xxx (xx.x%)	-
- 1	xxx (xx.x%)	-
- 2	xxx (xx.x%)	-
- 3 or more	xxx (xx.x%)	-
- Missing *(if applicable)*	xxx	-
At least one Treatment-Emergent Adverse Event (TEAE)	xxx (xx.x%)	xxx
At least one Serious Adverse Event (SAE)	xxx (xx.x%)	xxx
- Death	xxx (xx.x%)	xxx
- Life-threatening	xxx (xx.x%)	xxx
- Hospitalisation of Prolongation of Hospitalisation	xxx (xx.x%)	xxx
- Persistent or Significant Disability or Incapacity	xxx (xx.x%)	xxx
- Congenital Abnormality or Birth Defect	xxx (xx.x%)	xxx
- Medically Important	xxx (xx.x%)	xxx

	Patients	**AEs**
- Missing *(if applicable)*	xxx	xxx
Intensity: At Least One AE:		
- Mild	xxx (xx.x%)	xxx
- Moderate	xxx (xx.x%)	xxx
- Severe	xxx (xx.x%)	xxx
- Missing *(if applicable)*	xxx	xxx
Outcome: At Least One AE:		
- Recovered	xxx (xx.x%)	xxx
- Not yet Recovered	xxx (xx.x%)	xxx
- Unknown	xxx (xx.x%)	xxx
- Missing *(if applicable)*	xxx	xxx
At Least One AE Requiring an Administration of Concomitant Drug	xxx (xx.x%)	xxx

MedDRA dictionary version 16.0.
%: (n row / N safety population) * 100.
Source: Listing 16.2.7.1.

Table 14.3.3.2 Treatment Emergent Adverse Events - Overall Summary - Safety Population

Same as table 14.3.3.1

Table 14.3.3.3 Pre-injection Adverse Events by Primary System Organ Class and Preferred Term - Safety Population

	Total (N=xxx)
At Least One TEAE	xxx (xx.x%)
SOC 1	xxx (xx.x%)
- PT 1	xxx (xx.x%)
- PT 2	xxx (xx.x%)
…	
SOC 1	xxx (xx.x%)
- PT 1	xxx (xx.x%)
- PT 2	xxx (xx.x%)
…	

TEAE: Treatment Emergent Adverse Event.
MedDRA dictionary version 16.0.
%: (n row / N safety population) * 100.
Source: Listing 16.2.7.1.

Table 14.3.3.4 Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term - Safety Population

Same as table 14.3.3.3

Table 14.3.3.5 Serious Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term - Safety Population

Same as table 14.3.3.3

Table 14.3.3.6 Treatment Emergent Adverse Events with Relationship to DOTAREM® by Primary System Organ Class and Preferred Term - Safety Population

Same as table 14.3.3.3

Table 14.3.3.7 Listing of Deaths - Safety Population

Patient Number	Primary System Organ Class Preferred Term Description	Start Date & Time/	Seriousness/ Outcome	Intensity / Relationship to DOTAREM®	Administration of Concomitant Drug	Date of MRI Examination
xxxx	xxxxxxxxxxxxxxxxxxxxxxxx	mm/dd/yyyy hh:mm/	Death/	xxxxxxxxxxxxx/	xxxxxxxxxxxxx/	mm/dd/yyyy hh:mm
	xxxxxxxxxxxxxxxxxxxx	mm/dd/yyyy hh:mm	Life-threatening	xxxxxxxxxxxxxxx	Yes/No/	
	xxxxxxxxxxxxxxxxxxxx	xxxx			Yes/No	

Etc.

MRI: Magnetic Resonance Imaging.
MedDRA dictionary version 16.0.
Source: Listing 16.2.7.1.

Table 14.3.3.8 Listing of Serious Adverse Events - Safety Population

Same as table 14.3.3.7

Table 14.3.4.1 Renal Status during Follow-up Period - Safety Population

		Follow-up 1 (N=XXX)	**Follow-up 2** (N=XXX)	**Follow-up 3** (N=XXX)
Serum Creatinine (Raw Data)	n	xxx	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Missing *(if applicable)*	xx	xx	xx
Serum Creatinine (Change from Baseline)	n	xxx	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Missing *(if applicable)*	xx	xx	xx

SD: Standard Deviation.
Source: Listing 16.2.8.1.

Table 14.3.5.1 Medical Events except MRI Examination during Follow-up Period - Safety Population

		Follow-up 1 (N=XXX)	**Follow-up 2** (N=XXX)	**Follow-up 3** (N=XXX)
Surgery	n	xxx	xxx	xxx
	Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing *(if applicable)*	xx	xx	xx
Pro-Inflammatory Syndrom	n	xxx	xxx	xxx
	Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing *(if applicable)*	xx	xx	xx
Hepato-Renal Syndrom	n	xxx	xxx	xxx
	Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing *(if applicable)*	xx	xx	xx
Liver Transplant	n	xxx	xxx	xxx
	Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing *(if applicable)*	xx	xx	xx
Other	n	xxx	xxx	xxx
	Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing *(if applicable)*	xx	xx	xx

MRI: Magnetic Resonance Imaging.
%: (n row / n non missing) * 100.
Source: Listing 16.2.9.2.

Table 14.3.5.2 Contrast Media for MRI Examination during Follow-up Period - Safety Population

		Follow-up 1 (N=XXX)	**Follow-up 2** (N=XXX)	**Follow-up 3** (N=XXX)
MRI Examination	n	xxx	xxx	xxx
	Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing *(if applicable)*	xx	xx	xx
If Yes*	Gadobutrol	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

		Follow-up 1 (N=XXX)	**Follow-up 2** (N=XXX)	**Follow-up 3** (N=XXX)
	Meglumine Gadoterate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	….	…	…	…
	Without Contrast	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

MRI: Magnetic Resonance Imaging.
%: (n row / n non missing) * 100, except for multiple answers %: (n row / n with MRI examination) * 100.
*As multiple examinations with various GBCA are possible for each visit, the sum of percentage could be greater than 100.
Source: Listing 16.2.9.3.

Table 14.3.5.3 Medical Events except MRI Examination during Follow-up Period by Primary System Organ Class and Preferred Term - Safety Population

		Follow-up 1 (N=XXX)	**Follow-up 2** (N=XXX)	**Follow-up 3** (N=XXX)
Surgery	At Least One Surgery	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	SOC 1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	- PT 1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	- PT 2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	…			
Pro-Inflammatory Process				
Etc…				

MedDRA dictionary version 16.0.
%: (n row / N column) * 100.
Source: Listing 16.2.9.2.

7.3. Contents of clinical study report section 16.2

Listing 16.2.1.1 Visit Dates - All Included Population

Patient #	Country	Centre #	Date of MRI Examination	Date of Follow-up 1	Date of Follow-up 2	Date of Follow-up 3

MRI: Magnetic Resonance Imaging.

Listing 16.2.1.2 Premature Withdrawal - All Included Population

Patient #	Date of Withdrawal	Premature Withdrawal	Who Decided the Withdrawal	Reason of Withdrawal

Listing 16.2.1.3 Centre Characteristics and Radiological Activities

Centre #	Type	Radiological Fields or Specialities	Number of MR Equipments	Magnetic Field	Number of MR Examinations/Week	Usual Practices in MR Units	Duration of FU After MR Examination
01	Public	Neurology/Cardiology	2	1.5/1.5	156	Allergic History assessment/ Other Assessment: RAUPSE	< 30 min

MR: Magnetic Resonance ; FU: Follow-Up .

Listing 16.2.2.1 Protocol Deviations - All Included Population

Patient #	Deviation Term	Deviation Code

Listing 16.2.3.1 Analysis Data Populations - All Included Population

Patient #	Efficacy Population	Safety Population

Listing 16.2.4.1 Demographics - All Included Population

Patient #	Population Flag	Age (years)	Age (months)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Sex

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population ; BMI : Body Mass Index.

Listing 16.2.4.2 Magnetic Field in Tesla - All Included Population

Patient #	Population Flag	Magnetic Field (Tesla)

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population.

Listing 16.2.4.3 Current Renal Status - All Included Population

Patient #	Population Flag	Renal Function	Most recent Serum Creatinine (umol/L)	Most recent Serum Creatinine (entered)	Unit	Date	Estimated Creatinine Clearance (mL/min)	eGFR (mL/min/1.73m2)

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population ; eGFR: estimated Glomerular Filtration Rate.

Listing 16.2.4.4 Risk Factors and Patient History - All Included Population

Patient #	Population Flag	Risk Factor	Result	Specify

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population.

Listing 16.2.4.5 Previous Examinations with GBCA - All Included Population

Patient #	Population Flag	Previous Examination	Number of Examination	Examination Date	Product Class	Product Name	Volume Administered (mL)
001	AIP/EP/SP	No					
002		Yes	3	13MAR2002	Gadobutrol	GADOVIST®	10
002		Yes	3	15APR2003	Gadoterate Meglumine	DOTAREM®	20

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population.

Listing 16.2.4.6 Recent Surgery - All Included Population

Patient #	Population Flag	Surgery	Description
001	AIP/EP/SP	Yes	

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population.

Listing 16.2.4.7 Concomitant Medications - All Included Population

Patient #	Population Flag	Concomitant Treatment
001	AIP/EP/SP	XXXX

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population.

Listing 16.2.4.8 Indication of Current MRI Examination - All Included Population

Patient #	Population Flag	Classification	Sub Classification	Specify
001	AIP/EP/SP			

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population.

Listing 16.2.4.9 Premedication - All Included Population

Patient #	Population Flag	Premedication	Specify
001	AIP/EP/SP	Yes	XXXXX

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population.

Listing 16.2.5.1 DOTAREM® Administration – All Included Population

Patient #	Population Flag	Total Volume (mL)	Total Dose (mL/kg)	Type of Injection	Number of Injection	Nature of Package	Volume of Vial	Volume of Pre-filled Syringe
001	AIP/EP/SP							

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population.

Listing 16.2.6.1 Overall Quality of Images and Diagnostic Quality- All Included Population

Patient #	Population Flag	Image Quality	Comment	Diagnosis	Specify	Reason
001	AIP/EP/SP	Fair	XXXXX	Yes	XXX	
001	AIP/EP/SP			No		XXXX

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population.

Listing 16.2.7.1 Adverse Events - All Included Population

Patient #	Population Flag	Primary System Organ Class Preferred Term Nature of the Event	Start Date	Seriousness/ Outcome	Intensity / Relationship to DOTAREM®	Administration of Concomitant Drug	Date of MRI Examination with DOTAREM®
xxxx		xxxxxxxxxxxxxxxxxxxxxx	mm/dd/yyyy	Yes:Death/ not yet recovered	Moderate/Not related	Yes :xxxxxxx	mm/dd/yyyy
		xxxxxxxxxxxxxxxxxxxxx	mm/dd/yyyy	No/recovered	Mild/unknown	No	

Etc.

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population ; MRI: Magnetic Resonance Imaging.
MedDRA dictionary version 16.0.

Listing 16.2.8.1 Renal Status during Follow-up Period - All Included Population

Patient #	Population Flag	Date of MRI Examination with DOTAREM®	Follow-up Visit	Date of Last Renal Function Assessment	Serum Creatinine (umol/L)	Serum Creatinine (Entered)	Unit

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population ; MRI: Magnetic Resonance Imaging.

Listing 16.2.9.1 Nephrogenic Systemic Fibrosis Suspicion/Diagnosis - All Included Population

Patient #	Population Flag	Date of MRI Examination with DOTAREM®	NSF Suspicion	Source of Suspicion	Confirmatory Biopsy	Specify if No	Date of the Biopsy	Final Diagnosis of NSF	Specify if No

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population ; MRI: Magnetic Resonance Imaging ; NSF: Nephrogenic Systemic Fibrosis.

Listing 16.2.9.2 Medical Events during Follow-up Period except MRI examination - All Included Population

Patient #	Population Flag	Date of MRI Examination with DOTAREM®	Follow-up Visit	Date of FU Visit	Medical Event Category	Medical Event Date	Primary System Organ Class (Preferred Term) [Description]	Medical Event Specify

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population ; MRI: Magnetic Resonance Imaging ; FU: Follow-Up.
MedDRA dictionary version 16.0.

Listing 16.2.9.3 MRI examination during Follow-up Period - All Included Population

Patient #	Population Flag	Follow-up Visit	Date of FU Visit	Product ATC Name	Product Class	Product Name	Volume Administered (mL)	Date

AIP: All Included Population ; EP: Efficacy Population ; SP: Safety Population ; ATC: Anatomical Therapeutic Chemical ; FU: Follow-Up.
WHO DD dictionary version 2015.

8. REFERENCES

[1] Iverson C, Flanagan A, Fontanarosa PB, et al American Medical Association Manual of Style: A Guide for authors and Editors. 9th ed

ICH-E3 Note for Guidance on Structure and Content of Clinical Study Reports

9. APPENDICES