Guerbet

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PROTOCOL No. DGD 55-003

THE NSSAFE STUDY

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

Methodology:
Observational, descriptive and multinational post marketing study.

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THE NSsaFe STUDY
Study Protocol

CONTENT

ABBREVIATIONS

AE	Adverse Event
AIP	All Included Patients
eGFR	estimated Glomerular Filtration Rate
eCrCl	estimated serum Creatinine Clearance
EP	Efficacy Population
FUP	Follow-UP
GFR	Glomerular Filtration Rate
GBCA	Gadolinium Based Contrast Agent
i.e.	id est
MDRD study	Modification of Diet in Renal Disease study
MRI	Magnetic Resonance Imaging
MR	Magnetic Resonance
NSF	Nephrogenic Systemic Fibrosis
PMS	Post Marketing Study
SAE	Serious Adverse Event
SCr	Serum Creatinine level
SP	Safety Population
SPC	Summary of Product Characteristics

1. Background/introduction

DOTAREM® (Gd-DOTA) is a paramagnetic contrast agent for Magnetic Resonance Imaging (MRI) which has been marketed in numerous countries worldwide since 1989. In this molecule, Gadolinium is tightly bound to the DOTA ligand and becomes inaccessible to the external medium so that only its paramagnetic effect can be expressed. Numerous clinical trials have been performed with DOTAREM® to evaluate its tolerance and diagnostic contribution.
The product is registered and marketed for various indications including neurological, whole body and angiographic indications.
The usual dose of DOTAREM® for these examinations is 0.1 mmol/kg but a dose up to 0.3 mmol/kg is recommended for some brain-imaging indications. The recommended dose is 0.1 mmol/kg i.e. 0.2 ml/kg in adults, children and infants. In angiography, depending on the results of the examination being performed, a second injection may be administered during the same session if necessary. In some exceptional cases, as in the confirmation of isolated metastasis or the detection of leptomeningeal tumours, a second injection of 0.2 mmol/kg can be administered.
Despite the possible interest of plain Magnetic Resonance (MR) examinations in some pathologic circumstances, Gadolinium based products like DOTAREM® have widely demonstrated their superiority over plain MRI and also over other imaging modalities in numerous pathologies.

As of today, based on post-marketing surveillance, more than 15 million units of DOTAREM® have been dispensed. To date, irrespective of the dose, adverse events reported in clinical trials, as well as those spontaneously reported, consist of paresthesia, headaches, sensation of heat, cold and/or pain at the injection site, nausea, vomiting and skin reactions such as erythema, rash and pruritus. Rare anaphylactoid reactions have been reported. A recent post-marketing study[1] involving more than 24.000 patients has provided the largest analysis of tolerance, adverse reactions and diagnostic yield with the use of DOTAREM® since its introduction into clinical practice. AEs were noted in only 0.4% of the examinations and were mostly rated as minor.

The good tolerance of DOTAREM® is probably to be credited to the very high thermodynamic stability of the DOTAREM® macrocyclic complex where the toxicity of free Gd3+ ions is reduced by the ligand, DOTA, which has eight coordination sites for chelation. Due to this very high thermodynamic stability, there is no need of an excess of ligand which is used in certain Gadolinium contrast agent preparations to ensure absence of free Gd3+ in solution. DOTAREM® elimination is essentially renal by free glomerular filtration; its half time is comparable to iodinated contrast agents.
Several other Gadolinium complexes with various chemical structures are commercialized apart from DOTAREM®. Most of them have a linear structure and consequently a lower thermodynamic stability than DOTAREM® which is the only Gadolinium chelate to be macrocyclic and ionic.

Although Gadolinium-Based Contrast Agents (GBCA) are generally regarded as non-nephrotoxic in a healthy population, the safety issue of these agents remains controversial in the high-risk patients group and some studies recently suggested a potential risk of gadolinium-induced nephropathy in severe renal impaired patients [2,3,4,5]. In addition, it has been reported recently that a rare serious adverse reaction called Nephrogenic Systemic Fibrosis (NSF) may occur after exposure to gadolinium contrast agents in severe renal impaired patients. This new pathology was first described in the medical literature in 2000[6] and to date, several hundred cases have been diagnosed worldwide. In 2006, the link between NSF and gadolinium-based

contrast agents was made[7,8,9]. NSF is characterized by extensive thickening and hardening of the skin associated with skin-colored to erythematous papules that coalesce into erythematous to brawny plaques. Nodules are sometimes also described, flexion contractures with an accompanying limitation of range of motion can also occur. It seems that Gadolinium complexes with high thermodynamic stability such as DOTAREM® have lower risk of being associated with NSF and that the vast majority of published NSF cases were associated with linear compounds.

At present, the highest incidence of NSF in the high risk renal impaired population is estimated around 3-4 % for Gadodiamide, a linear Gadolinium complex with the lowest thermodynamic and kinetic stabilities among the Gadolinium chelates, but seems to be variable from one product to another. The European Medicines Agency and recently the Food and Drug Administration have classified the gadolinium-containing contrast agents in three groups according to NSF risk based on their thermodynamic and kinetic properties. DOTAREM® was placed in the low risk group.
To date, DOTAREM® is considered as one of the contrast agents with the lowest risk of NSF. In order to confirm this low risk, the incidence of NSF after injection of DOTAREM® must therefore be determined not only in patients with severe renal impairment, but also in patients with moderate renal impairment in order to provide an estimate covering a large population of renal impaired patients.

2. Study objectives

The main purpose of this study is to prospectively estimate the incidence of NSF in patients with moderate to severe renal impairment after administration of DOTAREM®. Secondarily, to collect a large number of data concerning the general safety profile of DOTAREM®, MRI indication, and conditions of use/administration of the product in this specific population of patients.
In addition, efficacy data (image and diagnostic quality) will also be recorded and described.
Regarding the safety profile of DOTAREM®, several follow-ups will be performed. After administration of DOTAREM®, patients will be followed during a two year period to assess if signs or symptoms suggestive of NSF have appeared.

3. Study design and methods

This observational Post Marketing Study (PMS) is a prospective transversal study including longitudinal safety follow-ups. This study will be performed in several European and non European countries. The sample size to be included is 1,000 patients with a minimum of 40% of patients with severe renal impairment. The number of sites and patients will vary from one country to another.
Fifty centres will be selected worldwide and each centre will able to include about twenty patients. Three to 5 centres will therefore be selected in each country, i.e. a potential recruitment of 60 to 100 patients per country.

This study will not modify the relationship between the patient and his/her physician(s), or the management of the patient follow-up. The patient will be orally asked if he/she agrees to participating in the study and provided with an information sheet about the study objectives and design, following local regulations. Patient's consent procedures will be followed according to each country's regulatory requirements.

3.1 Site selection

The selection of sites will be conducted by the local Sponsors.
In order to identify each participating site, the radiologist will have to fill in a dedicated form related to the site characteristics and radiological activities.
Data related to the sites profiles will be described and discussed at the time of study analysis.

3.2 Study population

Over a twenty-month period, each participating radiological site will include in this study patients (adults and children), who have moderate (eGFR 30-59 ml/min/1.73m^2) to severe (eGFR<30 ml/min/1.73m^2) and end stage (eGFR<15 ml/min/1.73m^2) renal impairment or dialysis, scheduled for a contrast enhanced MRI with DOTAREM® . A patient will not be included in case of contra-indication to MR examination or for any other criteria as defined below and in the product SPC (Summary of Product Characteristics) corresponding to the marketing authorization in each of the involved countries.

Patients will be included in the study following the criteria detailed below:

Inclusion Criteria

- Patient scheduled for a contrast enhanced MRI with DOTAREM® and who will be followed up for his/her renal impairment by one of the site study co-investigators.
- Patient must have moderate (eGFR 30-59 ml/min/1.73m^2) to severe (eGFR<30 ml/min/1.73m^2) and end stage (eGFR<15 ml/min/1.73m^2) renal impairment, dialysis patients can also be included.

Non-inclusion Criteria

- Patient who has pre-existing NSF or NSF like symptoms
- Patient who has received a GBCA within the past 12 months prior to inclusion in this study except if the GBCA received is DOTAREM®.
- Patient who has experienced a previous hypersensitivity reaction to GBCA.
- Pregnant woman or breast feeding woman

Patients will be recruited consecutively by radiologists, when a patient referred by a co-investigator attends the radiology department for MRI with injection of DOTAREM®.

3.3 Data collection

Each patient will be identified by a unique number in the study.
At the time of inclusion, some demographic and patient medical and biological history information will be collected by the radiological team on a dedicated electronic case report form.
These data will include the most recent available serum creatinine level and ionograms level (calcium, phosphates …)
The estimated Glomerular Filtration Rate (eGFR) (MDRD formula for adults) or estimated creatinine clearance (eCrCl) (Schwartz formula for children) will be calculated and reported on the form as well.

MDRD formula : (for adults only)

eGFR (ml/min/1.73m²) = 186 x $Cr^{-1.154}$ x $age^{-0.203}$ x k

where : k = 1 for males
k = 0.742 for females
k = 1.212 for black patients
Cr = creatinine (mg/dl)
age (years)

Schwartz formula : (for children only)

eCrCl (ml/min) = [k x height] / Cr

where : k = 29 for newborns
k = 40 for infants
k = 49 for children < 12 years old
k = 53 for girls (12-18 years old)
k = 62 for boys (12-18 years old)
height (cm)
Cr = creatinine (µmol/l)

The indication for the MRI examination will be specified on this form as well as data relative to DOTAREM® administration (volume, type of injection, number of injections, nature and volume of package used). The product will be administered under conditions strictly in accordance with the local product SPC.
Image and diagnostic quality will be assessed by the radiologist.
The Adverse Events (AE) occurring during the MRI examination or during the time of usual follow-up post DOTAREM® administration will be notified and described.
In any case of Serious Adverse Event (SAE), the radiologist will promptly inform the local Sponsor (local pharmacovigilance contact) using a dedicated "Suspect Adverse Reaction report" (F006031-See appendix)

All patients will be followed up during 2 years after DOTAREM® administration to collect data on any suspected NSF or NSF related symptoms. When the patient visits his/her physician for routine follow-up, a follow up study form will be completed by the physician in the electronic case report form. The physician will have to report:

- If any medical events have occurred since the last visit of the patient,
- If a renal function assessment has been done
- If there is any suspicion of NSF

In case of NSF suspicion, a biopsy could be decided by the medical team as a part of the normal patient follow-up in order to confirm or not the diagnosis of NSF. In such a situation, the biopsy results will be collected in a follow-up form.

If any case of suspicion/diagnosis of NSF, the physician in charge of the patient management will promptly inform the local Sponsor (local pharmacovigilance contact) using the dedicated "Suspect Adverse Reaction report" (F006031-See appendix).

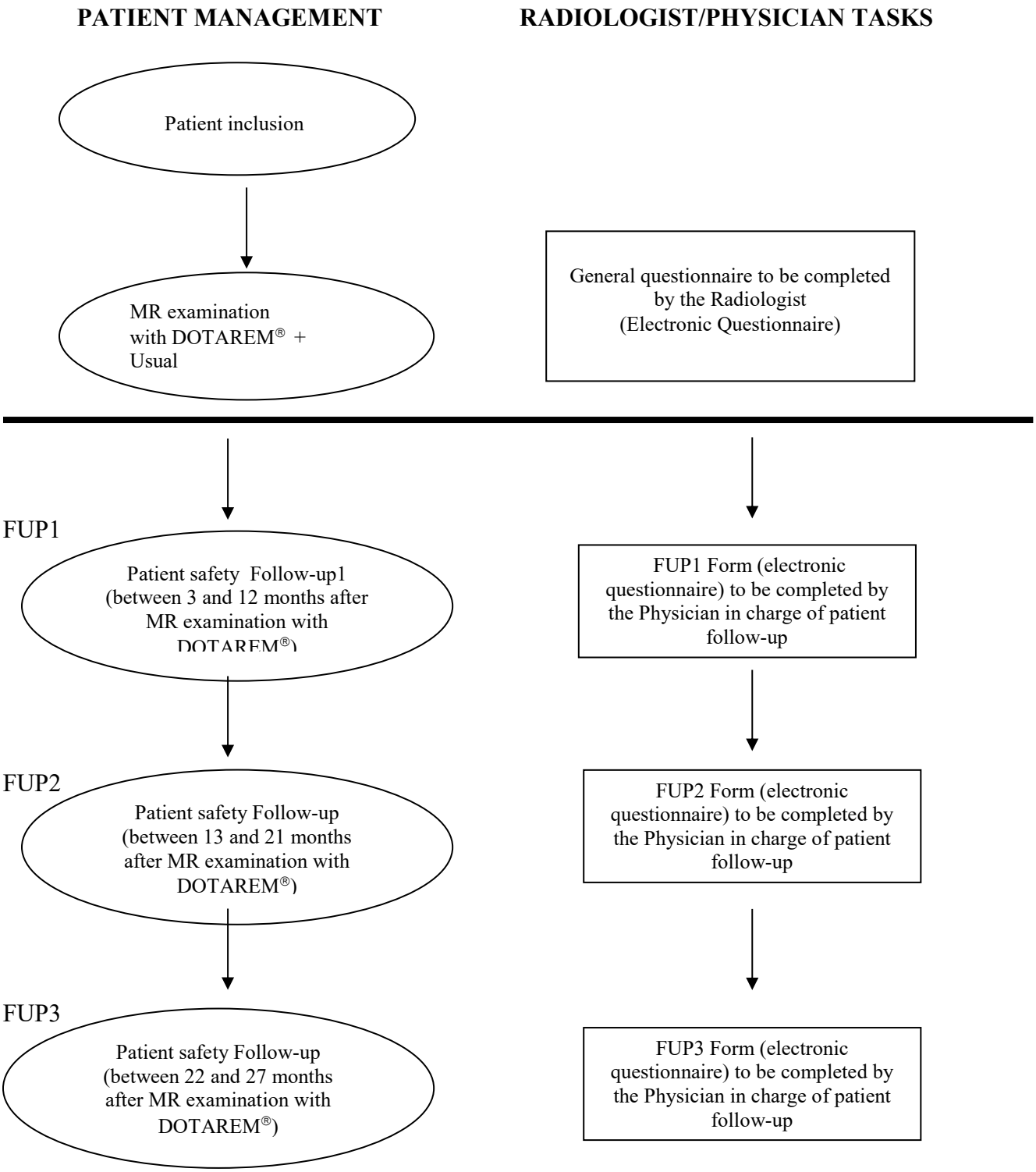
Three follow up visits will have to be reported as described below respecting patients' usual follow-up visits:
- FUP1: a visit occurring between 3 and 12 months
- FUP2: a visit occurring between 13 and 21 months
- FUP3: a visit occurring between 22 and 27months

Please note that there should be at least 3 months difference between each Follow-up visit reported in order to avoid redundant visits.

If no information could be obtained during the first year after DOTAREM administration from the patient, the physician in charge of the follow-up will be requested to check the hospital/medical notes of the patient and complete a follow up visit form with the data from the hospital notes. This will be requested again during the second year after the DOTAREM administration for the second follow-up and for the last follow-up as well.

The electronic questionnaire for patients of the same centre will be accessible by all investigators of the centre by using personalized logins and passwords. The electronic data collection system also allows follow-up of the changes made by each user.

3.4 Study Chart



4. Safety follow-up and procedures for reporting Serious Adverse Events (SAE)

For any patient included in this study, the radiologist will notify any adverse event occurring during the MRI examination or during the time of usual follow up post DOTAREM® administration.
A Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

-Results in death
-Is life-threatening
-Requires hospitalisation or prolongation of existing inpatients' hospitalisation,
-Results in persistent or significant disability or incapacity
-Is a congenital anomaly or birth defect
-Is medically significant : important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

In any case of Serious Adverse Event (SAE), during the MRI examination or during the time of usual follow-up post DOTAREM® administration the radiologist will promptly inform the local Sponsor (local pharmacovigilance contact) immediately and within no more than 24 hours of knowledge using a dedicated "Suspect Adverse Reaction report" (F006031-See appendix)

If any case of suspicion/diagnosis of NSF occurring during the study until the 2 year FUP period, the physician in charge of the patient follow-up will promptly inform the local Sponsor (local pharmacovigilance contact) using the dedicated "Suspect Adverse Reaction report" (F006031-See appendix).

Additional information (e/g. autopsy, lab reports…) may be required by the Sponsor in a timely fashion to ensure accurate follow-up and assessment of each case and should be forwarded with a new form specifying basic information (follow-up number, patient details and number, AE, study product, causal relationship) and the new information.
The initial and follow up reports shall identify the study subject by his/her Identification Number assigned for the purpose of the trial.

In order to allow the assessment and eventual subsequent regulatory reporting of the case, the following minimum information should be filled in:
- Patient's details including age, sex and patient's trial enrolment number assigned in the study (to be reported in section "information concerning the reaction"-description),
- Patient's medical history relevant to the assessment of the reaction
- Type of the reaction by reporting a diagnosis or if not available, symptoms
- Date and time to onset of the reaction
- End date of the reaction (will be reported in a follow-up report if the reaction is still ongoing at the time of first notification)
- Name of the drug related to the examination or procedure in cause, date and time of administration, dose administered
- Causal relationship to the drug related to the examination or procedure in cause (mandatory)
- Outcome (no recovery/ recovery / recovery with sequelae/ unknown/death).

Event leading to a SAE report should be reported in the AE section of the case report form.

SAEs should be followed up by the Physician until complete recovery of the patient or, if not possible, until stabilisation of sequelae. The Physician may be requested by the Sponsor to provide follow-up information in order to comply with current regulations as well as for comprehensive assessment purposes.

If a serious event occurs, the Physician is responsible for the measures to be taken to ensure the safety of the study participants.

In addition, if occurring after the end of the patient's follow-up period, SAEs that the Physician thinks may be associated with the study medication/procedure must be reported to the local Sponsor (local pharmacovigilance contact) regardless of the time between the event and the end of the study.

According to local requirements, the Sponsor will communicate relevant safety information to the appropriate agency(ies), International Review Board / Independent Ethics Committee and/or all active investigators, as it becomes available.

The transmission of the information to the Sponsor does not release the Physician from his/her responsibility to inform the regulatory authorities, if applicable.

5. Statistics / Data analysis

For data analysis purposes, all the data will be collected in electronic format. Any electronic database provided will be compatible with an SAS format that will be used for statistical analysis.

The following section summarizes the statistical analysis method which will be fully described in the Statistical Analysis Plan.

5.1 Overview

Quantitative variables will be summarized in tables including sample sizes, means, standard deviations and extreme values as well as medians and percentiles when appropriate.
Qualitative variables will be described in terms of frequencies and percentages of the number of individuals considered.

5.2 Statistical tests

Two-sided tests will be performed at a 5% level of significance. In case of multiple comparisons or criteria and when appropriate, the significance level of each test will be adjusted to the total number of comparison to ensure a 5% overall significance level.
Accuracy of estimates will be calculated with two-sided 95% confidence intervals.
Gaussian quantitative variables will be analyzed using Student-t-test or F-test depending on the number of means involved.
Non Gaussian quantitative variables and ordinal qualitative variables will be analyzed using Wilcoxon's test.
Nominal qualitative variables will be analyzed using Chi-square test or Fisher's exact test.

5.3 Populations of analysis

There will be 3 patient populations defined for this study : all-included-patients (AIP), the safety population (SP) and the efficacy population (EP).

The all-included-population (AIP) will include all patients enrolled in the study and having a questionnaire partly or fully filled in. This population will be used for the description of demographic data and medical history of patients and the indication for MRI.

The safety population (SP) will include all patients exposed to the contrast product and having received at least one injection of contrast agent, regardless of the quantity. This population will be used to describe for all the safety parameters, administration modalities, adverse events and laboratory data.

The efficacy population (EP) will include all patients who have been imaged and who have an available diagnostic assessment. This population will be used to describe the image quality and the diagnostic quality.

5.4 Data analysis for global population

The minimum number of patients included in this study will be 1000 (see next section). Several levels of aggregating patient data will be explored in the statistical analysis and summarized statistics will be reported at :

- centre level within countries;
- country level;
- overall (adjusted on countries if the heterogeneity between countries is too high).

5.5 Power and sample size calculation

This is a study which aims at accurately estimating the incidence of the NSF in renal impaired patients, in case of such an event being observed after injection of DOTAREM®. Assuming that when exposed to Gadolinium, the frequency of NSF is ranging from 0% to 4% in this population (maximum frequency observed for a linear gadolinium), with a sample size of 1000 subjects, 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	Expected frequency	Exact 95% IC	Accuracy (max extent from expected frequency)	Poisson Law – Proba. At least 1 case if expected freq.
0	1000	0.0%	0.00% - 0.37%	0.4%	-
1	1000	0.1%	0.00% - 0.56%	0.5%	63%
2	1000	0.2%	0.02% - 0.72%	0.5%	86%
5	1000	0.5%	0.16% - 1.16%	0.7%	99%
10	1000	1.0%	0.48% - 1.83%	0.8%	100%
15	1000	1.5%	0.84% - 2.46%	1.0%	100%
20	1000	2.0%	1.23% - 3.07%	1.1%	100%
30	1000	3.0%	2.03% - 4.26%	1.3%	100%

Explanation of the table:
The incidence of NSF in high-risk subjects (renal impairment) exposed to DOTAREM® is unknown. The table therefore investigates the probability of observing the event of interest (development of NSF) in a cohort of 1,000 patients with renal impairment, prospectively considered to be a sufficient sample size.
The first column of the table indicates the number of cases that would be hypothetically observed in the cohort, column 3 transforms the number of cases to a percentage, column 4 is the exact confidence interval (according to the binomial law) of this calculated percentage, column 6 indicates the probability of observing, in a sample of 1,000 subjects, the number of cases indicated in column 1, according to the Poisson law (rare event, considered not as a percentage but as a number).
Line 1 of the table indicates that, when 0 cases are observed in the cohort, the Poisson law cannot provide a probability estimate, while the binomial law indicates that 0 observed cases is not incompatible with a frequency of the event significantly different from zero.

5.6 Potential number of patients lost to follow-up

The potential number of patients lost to follow-up was estimated by considering that a loss of 10% of the sample size would be acceptable (100 subjects), corresponding to a minimum observable frequency of 0.111% instead of 0.1% in 1,000 subjects. If the number of patients lost to follow-up exceeds 100 subjects, the protocol will be amended to revise the sample size.

5.7 Information about the study results

The study report will include all the study analysis performed and will be provided to the participating investigators if needed.

6. Study timetable

Depending on countries/sites, the study will take place starting in the first quarter 2011 and patient recruitment will last until the second quarter of 2014. Patients will be followed over a two year period after DOTAREM® administration.

7. Regulatory issues/ Quality Assurance

The study will be conducted in each participating country in accordance with the local regulations in force.
The patient will be orally asked if he/she agrees to participating in the study and informed about the study objectives and design. Patient's consent procedures will be followed according to each country's regulatory requirements.
The Sponsor reserves the right to perform an audit of the study data in order to verify the quality of their collection, their security and their integrity.
Each participating physician will sign a financial agreement specifying his/her commitment to respect the study protocol and the amount of fees that he/she will receive for the study.

8. Confidentiality

The physician and all staff involved must respect professional secrecy regarding the nature of the product studied, the way in which the study is carried out, the people participating and the study results obtained.
No information that could allow an identification of the patient identity will be collected. Patient confidentiality will be maintained at all time (by Sponsor, Clinical Research Organisation, Regulatory Authorities, Ethics Committees).

9. Publications

The study data are the exclusive property of the Sponsor. No data can be published by the physician without prior approval by the Sponsor in writing. The modalities concerning the publications and the presentations about the study results will be defined by the Sponsor.

10. References

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[6] Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE (2000). "Scleromyxoedema-like cutaneous diseases in renal-dialysis patients". Lancet 356 (9234): 1000–1.

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[9] Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents--St. Louis, Missouri, 2002-2006". MMWR Morb. Mortal. Wkly. Rep. 56 (7): 137–41. 2007

11. Physician signature

I have read this protocol and agree to conduct the study as described in agreement with local regulations. I will provide copies of the protocol and all the required information to the physicians involved and to all the personnel under my supervision who could participate in this study. I will ensure that they are fully informed regarding the study conduct.

Name and address of the institution:

Physician's Signature **Date** : |___|___| |___|___| |___|___|___|___|

Day Month Year

Printed Name:

12. Appendices

Appendix 1: Form related to site characteristics and radiological activities
Appendix 2: Patient general questionnaire
Appendix 3: Patient FUP questionnaire**.**
Appendix 4: Suspect Adverse Reaction Report (F006031)
Appendix 5: Patient Information Sheet