European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT FOR SINEREM

International Nonproprietary Name (INN):
superparamagnetic iron oxide nanoparticles stabilised with dextran and sodium citrate

Procedure No. EMEA/H/C/801

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AMI	Advanced Magnetics Inc.
APTT	Activated Partial Thromboplastin Time
AUC	Area Under Curve
BMS	Bristol-Myers-Squibb
Cl	Clearance
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
EAU	European Association of Urology
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
FN	False Negative
FP	False Positive
GCP	Good Clinical Practice
GE	Gradient Echo
H&N	Head and Neck
IIS	Investigator-Sponsor Initiated Studies
LN	Lymph Nodes
MEDIC	Multiple Echo Data Imaging Combination
MPS	Mononuclear Phagocytic System
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NK	Natural Killer
NPV	Negative Predictive Value
OR	Odds Ratio
PAE	Patient Adverse Event rate
PET	Positron Emission Tomography
PLND	Pelvic Lymph Node Dissection
PPV	Positive Predictive Value
PSA	Prostate Specific Antigen
PT	Prothrombin Time
ROC	Receiver Operating Characteristics
SAE	Serious Adverse Event
ScARG	Scientific Advice Review Group
ScA	Scientific Advice
SE	Spin Echo
Se	Sensitivity
Sp	Specificity
SmPC/SPC	Summary of Product Characteristics
SPIO	Super Paramagnetic Iron Oxide
TIBC	Total Iron Binding Capacity
T ½	Half life time of elimination
TN	True Negative
TNM	Tumour Node Metastasis
TP	True Positive
US	Ultrasonography
USPIO	Ultrasmall Super Paramagnetic Iron Oxide
Vd	Distribution volume
WBC	White Blood Cells

GLOSSARY

Sinerem-enhanced MRI	Either the MR procedure performed after Sinerem infusion, or the reading of the images of this procedure, taking into account the effect of Sinerem on the MR images. May also be called “MRI with Sinerem” or “post-Sinerem MRI”
Un-enhanced MRI	Either the MR procedure performed before any Sinerem injection and which serves as the reference technique to the Sinerem-enhanced MRI, or the reading of the images of this procedure. May also be called “plain MRI” or “pre Sinerem MRI” or “MRI without Sinerem”. In some trials it may be a sequence insensitive to Sinerem® performed during the same procedure as the Sinerem-enhanced MRI
Paired MRI	Reading of the images to evaluate Sinerem using Sinerem-enhanced images, and un-enhanced images as a reference (diagnosis based on signal change)
Post-alone MRI	Reading of the images to evaluate Sinerem using only the Sinerem-enhanced MR images, where the lymph node signal is assessed using the surrounding tissue as the reference. May also be called “post Sinerem only”
Reader diagnosis	Diagnosis based on all criteria available on images (i.e. type of primary tumour, number of lymph nodes, size, shape, etc ...). May also be called “subjective diagnosis”
MRI diagnosis	Diagnosis based on lymph node size (for un-enhanced MRI) and signal difference (for Sinerem) criteria. May also be called “objective diagnosis”
Patient unit	Evaluation of the patient taken as a whole, taking into account all lymph nodes (visualised or not on MRI)
Lymph node unit	Evaluation of lymph nodes individually correlated to histology

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQs on quality, safety and efficacy, the CHMP consider that the application for Sinerem, in diagnostic use only for the characterisation of lymph nodes visualised with MRI (Magnetic Resonance Imaging) in the evaluation of primary tumour spread in pelvic cancers is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Proposal for Questions to be posed to additional Experts
Not considered necessary

Inspection issues
The site of active substance manufacture was inspected by France's authorities in June 2007 and was found to be compliant with EU GMP.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Together with cardiovascular disease, cancer is currently one of the main causes of death in Europe. In 2004 in the European Union, there were over two million (2,060,400) incident cases of cancer diagnosed and over one million cancer deaths (1,161,300). The most common incident form of men cancer was prostate cancer (202,100 cases, 18.1% of all incident cases), bladder cancer represented the fourth most common form (91,000 cases, 8.2%), after lung and colorectal cancer. In women there were 81,500 incident cases of uterus cancer (8.6%), the 3rd most common form after breast and colorectal cancers.

Cancer patient prognosis depends on the histopathological grade, size and extent of the cancer, as well as the age and performance status of the patient. Following diagnosis, determination of the extent of cancer remains one of the most critical issues for both the patients and clinicians responsible for selecting an appropriate treatment. Distinguishing newly diagnosed patients with confined localised cancer from those whose cancer has spread to the lymph nodes or more distant sites is important since the corresponding therapies may differ radically. For the same reason, distinguishing local residual or recurrent disease from nodal or distant metastases in post-surgery or post-radiotherapy settings is equally important.

In order to select the most appropriate type of management for a particular patient, the primary tumour is assigned a stage. Staging forms the basis of initial patient management and also provides a guide to prognosis.

The most commonly used staging method, in particular in pelvic cancers, is the Tumour, Nodes, Metastasis (TNM) system. Each stage describes the state of pathological development of the tumour. The nodal stage (N) reflects the spread of the disease to lymph nodes. The overall stage is based on a combination of these T, N, and M parameters.

Clinical staging, which is based mainly on the clinical examination, imaging modalities and biological markers when suitable, should be differentiated from pathological staging, which is an adjustment of clinical staging, based on surgical and histopathological findings.

Clinical staging is essential as it is the basis upon which the patient diagnosis and therapeutic strategy are established. This staging will serve to decide whether surgery is indicated or not, what type and extent of surgery is appropriate, whether surgery must be preceded by chemotherapy, and whether adjuvant therapy is indicated.

In this clinical staging, evaluation of the nodal stage is very important and varies according to the type of tumour.

In pelvic cancer, clinical N stage is rated as follows:

- Nx: Regional LN have not been assessed
- N0: No regional LN metastasis
- N1: Regional LN metastasis

Histopathological staging is much more precise. As an example, N is rated as follows in bladder cancer:

NX Regional LN cannot be assessed
N0 No regional LN metastasis
N1 Metastasis in a single LN 2 cm or less in greatest dimension
N2 Metastasis in a single LN more than 2 cm but not more than 5 cm in greatest dimension, or multiple LN, none more than 5 cm in greatest dimension
N3 Metastasis in a LN more than 5 cm in greatest dimension

Depending on the primary tumour location, the treatment strategy is determined by consensus or, conversely, may vary widely according to countries or even to centres. In all cases, nodal involvement and the extent of nodal involvement will strongly influence this treatment strategy for the pelvic cancer patient:

- There is a consensus to exclude prostate cancer patients from surgery if a frozen section shows LN metastases.
- Non-invasive bladder tumours benefit from transurethral resection with or without adjuvant treatment, while invasive bladder tumours are treated by cystectomy, which may be radical or not according to overall status and age, bladder-sparing surgery together with neoadjuvant or adjuvant chemotherapy and/or radiation which is a reasonable alternative to radical cystectomy. The European Association of Urology recommends limited LN dissection, as no controlled studies exist supporting the curative value of LN dissection. The results of LN staging strongly influence the conduct of the surgical procedure.
- There are many established algorithms for the treatment strategy in cervix and corpus uteri cancers. In brief, small sized N0 tumours benefit from tumour surgery alone, while larger sized tumours and N+ tumours require tumour surgery in association with lymphadenectomy (the extent of which varies according to the number of invaded LN), as well as chemotherapy and/or radiotherapy.

Apart from the clinical examination, precise definition of lymph node involvement has to be based on imaging modalities, such as computed tomography (CT), conventional MRI, ultrasonography (US) or endoscopic ultrasonography, Positron Emission Tomography (PET), the fusion of PET and CT. It is widely accepted that none of these imaging modalities are entirely satisfactory. The evaluation criteria proposed are all morphological criteria, which are not specific for either lymph nodes or the tumour. They mainly consist of the size of the lymph node, a short-axis diameter above 10 mm for oval nodes and 8 mm for round nodes being generally used to define a malignant lymph node. This criterion is known to lack sensitivity, due to the fact that metastases may be present in normal-sized lymph nodes, and specificity, as large lymph nodes may be either metastatic or inflammatory. Other criteria, such as the presence of necrosis, the shape of the lymph node, the number of nodes visualised and the presence of fat, have been proposed, but do not necessarily improve the diagnostic performance of the technique. Although promising, enhancement pattern using iodine at CT and gadolinium chelates at MRI has met the same limitations. Thus, an invasive diagnostic method (lymphadenectomy) is still regarded as the routine standard for establishing potential lymph node involvement and serves as the basis for the final therapeutic decision. Nevertheless this method can itself present some false positive and false negative results.

Several authors report that extended pelvic lymphadenectomy is associated with a high rate of lymph node metastasis outside of the fields of standard lymphadenectomy in cases of clinically localised prostate cancer.

In summary, detecting tumorous lymph nodes preoperatively in pelvic cancers is now the most challenging issue for both surgeons and radiologists. As seen before, extended dissection of pelvic lymph nodes is an efficient tool for detecting occult micrometastases in lymph nodes. However, this dramatically lengthens the surgical procedure time and carries a higher morbidity rate than limited nodal dissection or tumour resection alone. Because the life expectancy of patients has improved in the past years, surgeons now have to manage patients who are older than before and to analyse the risks and benefits of surgery in such patients. In younger patients, the consequences of any surgical procedure in terms of quality of life are becoming more prominent than before and have to be taken into account such as:

- will surgery preserve sexual function in male patients?
- is there any risk of lymphocele or lower limbs oedema?
- is there any risk of denervation?

Due to the specific cellular uptake of Sinerem into the macrophages in normally functioning nodes, and the lack of reticuloendothelial activity in metastatic nodes which cannot take up USPIO (ultrasmall super paramagnetic iron oxide), it was assumed that Sinerem could help differentiate between healthy and malignant LN and thus provide a non-invasive and more accurate diagnostic tool for cancer patients.

Various MRI experimental studies performed in animals with Sinerem validated the following hypothesis:
- normal, or inflammatory lymph nodes present a signal decrease on T2-weighted sequences,
- metastatic lymph nodes do not present any signal change in the majority of cases due to invasion of tumor cells/tissue into the healthy macrophages. A high-intensity signal has sometimes been observed, attributed to tumour neovascularisation and to the T1 effect of particles present in the free state in the vascular space.

Guerbet decided to set up a clinical development programme to demonstrate the efficacy and safety of Sinerem-enhanced MRI in the detection of lymph node metastases in pelvic cancer patients.

II.2 About the product

Sinerem is a new contrast agent for Magnetic Resonance Imaging (MRI) developed for marketing by GUERBET: Pharmacotherapeutic group: Intravascular contrast agent for MRI (iron oxide nanoparticles), ATC code: V08C B03. It is administered in humans as a single dose by intravenous infusion. Guerbet is applying for the Marketing Authorisation of Sinerem in the characterisation of lymph nodes (LN) visualised with MRI (Magnetic Resonance Imaging) for evaluation of primary tumour spread in pelvic cancers.

Sinerem belongs to the group of contrast agents specific to the reticuloendothelial system (liver, spleen, lymph nodes, bone marrow), mainly represented by iron oxide nanoparticles coated with macromolecules such as dextran in the presence of adjuvants (mineral salts, polyhydric alcohols, etc.). Two sub-groups can be differentiated on the basis of particle size:

- The SPIO (Super Paramagnetic Iron Oxide) sub-group (mean particle diameter approximately 150 nm) which includes Endorem, a contrast agent marketed by GUERBET.
- The USPIO (Ultrasmall Super Paramagnetic Iron Oxide) sub-group (mean particle diameter 30 nm), which includes Sinerem, the subject of the present overview.

Sinerem, because its smaller particle size results in vascular remanence and uptake by the macrophages of organs such as the lymph nodes, will be used for the diagnosis of lymph node metastases. The maximal dose taken up by the liver and the lymph node has been shown to be respectively 2%/g and 43%/g for Sinerem, while it was 6% and <1% for Endorem.

As shown by its low Relaxivity R_2 (37°C; 20 MHz) i.e. 53 $mmol^{-1}$ s^{-1}, Sinerem has a strong T2 relaxivity, which leads to a strong decrease in the signal intensity (negative enhancement) of various target organs on T2-weighted images. In addition, Sinerem also has a high T1 relaxivity, which may result in an additional increase in signal intensity on T1-weighted images.

Sinerem shows a specific cellular uptake by the macrophages in normally functioning nodes and reduces the signal intensity of tissue in which the particles accumulate. In metastatic nodes, cancer cells, which lack reticuloendothelial activity and cannot take up USPIO, replace macrophages; these metastatic nodes maintain their signal intensity.

The proposed indication of Sinerem is:

- For diagnostic use only

- Characterisation of lymph nodes visualised with MRI (Magnetic Resonance Imaging) in the evaluation of primary tumour spread in pelvic cancers

The product is indicated for intravenous administration only (infusion). The recommended dose is 2.6 mg Fe/kg body weight (45 µmoles Fe/kg) i.e. 0.13 ml/kg body weight of reconstituted freeze-dried preparation. The contrast agent should be administered via the infusion filter by slow intravenous infusion (4 ml/min) over a period of about 30 minutes, after dilution in 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, 24 to 36 hours before the MRI procedure.

Due to the absence of clinical experience in children, Sinerem should not be administered to patients under the age of 18 years.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The clinical development of Sinerem started with a first set of clinical trials, conducted from Phase I in 1992 to Phase III in 2006, in various indications involving lymph node metastases. Having established the pharmacokinetics of Sinerem and the choice of effective dose a first programme of Phase III trials in lymph node cancer imaging was then set up with one or two trials per organ in pelvis, head and neck, lung, rectal and breast cancers.

In addition, CHMP Scientific Advice was sought on the appropriate clinical development to better demonstrate the efficacy of the product to characterise metastatic lymph nodes in pelvic cancers in MRI.

Compliance with CHMP Guidance and Scientific Advice were applied in:
- Conducting single pivotal study (ALS 44 003),
- The applicant calculated sensitivity as well as specificity (as primary endpoints) and positive and negative predictive values (as secondary endpoints) in line with CHMP guidance “Points to consider on the evaluation of diagnostic agents” (CPMP/EWP/1119/98)

As summarised in the following table, in total the current application presents 37 clinical trials. The studies comprise 2 controlled phase III studies in the proposed indication (ALS 44 003, ALS 3 7), 1 controlled phase III study in a broader patient population (38804-10) and 15 uncontrolled studies, including 6 in the proposed indication.

Table: Clinical trial efficacy and safety data considered for the current application

Sinerem Clinical trials	Number of studies	Number of patients
EFFICACY		
Controlled* phase III LN studies in pelvic indication	2	327
Other controlled* Phase III LN study including pelvic indication	1	166
Other Phase II/III LN studies including pelvic indication	6	296
Phase II/III LN studies excluding pelvic indication	9	335
SAFETY		
Pharmacokinetic and pharmacodynamic studies	5	147
Phase II/III studies in the pelvic LN indication	5	378
Phase II/III studies in LN in other anatomical regions and other indications	28	1252

* controlled: comparing Sinerem-enhanced MRI to unenhanced MRI, on the basis of a centralized off site reading, using the patient as his own control, referring to histopathology as the gold standard

There is no clinical experience in children.

II.4 General comments on compliance with GMP, GLP, GCP

GMP
Satisfactory manufacturing licences have been provided for the sites of finished product manufacture and batch release; therefore GMP inspections are not required prior to MA approval for these sites.

GLP and GCP
The applicant has stated that all trials were GLP and GCP compliant.

II.5 Type of application and other comments on the submitted dossier

The application has been submitted under Article 8.3 of Directive 2001/83/EC, as amended (complete and independent application). The applicant has not requested an accelerated assessment, conditional approval or exceptional circumstances.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The drug substance is an aqueous colloidal solution of nanoparticles of iron oxide which have superparamagnetic properties.

The manufacturing process for the active substance has been described satisfactorily. The proposed specification for the active substance is suitable for its control with respect to its physical and chemical properties. Information has been provided in relation to the microbiological properties of the drug substance

Stability trials on four pilot and three production scale batches of the active substance are in progress, with up to 12 months of long-term and accelerated data available for all batches. Results

demonstrate the instability of the substance and the requirement for storage at 5 ± 3 °C. The proposed retest date for the active substance is 12 months, with the storage conditions: 'store and transport refrigerated'. This is considered acceptable. One production lot per year of manufacture will be entered into long-term stability studies according to the protocol provided. This is acceptable.

Drug Product

The product is available in 1.0 and 1.5 g presentations. The development of the product has been described, the choice of excipients is justified and their functions explained. Confirmation that all of the clinical batches complied with the current proposed specification was requested and provided. The manufacturing process is described adequately

The product specifications cover appropriate parameters for the product. Validation data for the analytical methods have been presented. Batch analysis has been performed on nineteen batches of the finished product. The batch analysis results show that the finished product meets the proposed specification.

Stability trials have been started at 25 ± 2 °C (long-term without humidity control), 25 ± 2 °C/60 % RH (long-term), 30 ± 2 °C/65 % RH (intermediate) and 40 ± 2 °C/75 % RH (accelerated). Six months of data under all conditions are presented for the 1.5 g batches whereas twelve months of accelerated data (40 °C/75 % RH) and thirty-six months of long term data (25 °C/60 % RH) are provided for the 1.0 g batches. Testing is performed in line with the finished product shelf life specification, which is identical to the release specification.

The proposed shelf life for both the 1.0 and 1.5 g presentations is 36 months with no special storage conditions. This is justified based upon the data generated for batches of the 1.0 g presentation, however a commitment to report any out-of-specification results in the ongoing stability trials for the 1.5 g presentation is requested.

III.2 Non clinical aspects

Pharmacology

Sinerem is indicated for the characterisation of lymph nodes visualised with MRI (Magnetic Resonance Imaging) in the evaluation of primary tumour spread in pelvic cancers. Since Sinerem is designed for diagnostic use only, the activity of interest is its effect on the magnetic resonance signal. Non-clinical studies on pharmacology or primary pharmacodynamics have not been conducted since there is abundant literature available and it has been established during clinical development.

The active substance is superparamagnetic iron oxide nanoparticles stabilised with dextran and sodium citrate. The size of the particles, 30nm, classifies the particles as USPIO. The size of the nanoparticles allows their entry into the reticulo-endothelial system. The nanoparticles are mainly taken up by macrophages in lymph nodes. The superparamagnetic nanoparticles are attracted to a magnetic field but retain no residual magnetism after the field is removed. Regions of the body that contain the superparamagnetic contrast agent appear darker in a MRI than regions without the agent. In healthy lymph nodes, cells of the phagocytic system (macrophages) can take up the particles whereas diseased lymph nodes do not have macrophages and cannot take up the contrast agent. Therefore the healthy lymph nodes are darkened although the diseased regions remain bright.

Since Sinerem is for diagnostic use only, secondary pharmacology was not investigated. Clinical studies investigating immune function revealed that Sinerem did not adversely effect immune function.

The safety pharmacology studies were conducted according to standards prevailing between 1990 and 1998. In vitro investigations of QT interval prolongation were not required at that time. Up to the dose level of 13 mg Fe/kg i.e. 5 times the intended human dose, Sinerem did not have major effects

on the CNS or respiratory systems in the rat. There were no effects on the ECG or haemodynamic parameters at the dose levels up to 2.6 and 20 mg Fe/kg in rats and dogs respectively. In rats at 13 mg Fe/kg a trend towards an increase in aortic and renal blood flows and a decrease in renal resistance occurred in some animals. In dogs at 200 mg Fe/kg slight and transient variations of some cardiac and renal parameters occurred in some animals but without a clear relationship to treatment.

Pharmacokinetics

The pharmacokinetic fate of particulate contrast agents is known to be governed by the reticuloendothelial system and the pharmacokinetics can be influenced by modifying the size and/or the coating of the particle. In the case of Sinerem, the small particle size allows an uptake not only by the Kupffer cells in the liver, but also uptake by the macrophages such as the lymph nodes.

All studies were conducted with one formulation and results were considered to be valid for an additional formulation in view of the very slight differences in composition between the two (involving only the excipient) and the results of a bridging study.

The studies confirmed that the lymph nodes were the organs with the highest uptake of the product. Following i.v. administration, the ^{59}Fe concentrations slowly decreased in the plasma showing the slow uptake of the particles by the macrophages. The distribution in organs was via the macrophage system with the highest concentrations being found in the spleen, liver and lymph nodes. The dextran coating was degraded before being eliminated mostly in the urine, whilst the iron was incorporated in haemoglobin before being very slowly eliminated mainly in the faeces as for endogenous iron.

When the pharmacokinetic parameters were compared, the monkey was more representative than the dog of the human situation and was therefore chosen as the non-rodent species for repeated dose toxicity study.

The issues concerning the pharmacokinetic studies are the dose levels used and the fact that the studies were single dose only.

The dose levels used were low in the studies with the unlabelled compound in the rat and monkey and for the studies in the rat with ^{59}Fe-labelled product compared to the proposed clinical dose. The applicant's experts stated that this can be explained by the changes made to the diagnostic dose during clinical development. Since in the rat a dose close to the diagnostic dose and a higher dose (2.3 and 3.4 mg Fe/kg respectively) of the ^{59}Fe-labelled product was studied as was the dose of 3.4 mg Fe/kg of the ^{14}C-labelled product, additional studies were not deemed necessary. No dose-effect was observed on pharmacokinetic parameters in humans. However, in the monkey the dose level used was 1.7 mg Fe/kg hence the systemic exposure in the toxicology studies is not known.

Single dose only studies were conducted although repeated dose toxicity studies were carried out. The applicant states that single dose only studies were conducted since these are the proposed clinical conditions of use. This may be acceptable since the toxic effects in the animal studies were probably related not only to the plasma concentrations of Sinerem but to the accumulation of iron in the body. The applicant compared the NOELs and NOAELs in the repeated dose animal studies with the human dose based on the cumulative dose levels.

Secretion into maternal milk was not investigated in either animals or humans. Consequently breast feeding should be discontinued if the product is to be administered during this period.

Toxicology

All studies were conducted in compliance with GLP. In all studies the route of administration was the same as that intended for clinical use i.e. intravenous.

Although the proposed clinical use is single use only, the non-clinical safety evaluation included 4-week repeated dose toxicity studies in rats and monkeys. The choice of the monkey as the non-rodent

species was based on the pharmacokinetics of Sinerem which was considered to be more relevant in the monkey than in the dog when compared to human data.

The acute toxicity was low in rats and dogs. Acute toxicity was observed only at very high dose levels i.e. 400mg Fe/kg, which is approximately 154 times the intended human dose, and was related to large dose of iron administration. The findings were similar in both species and consisted principally of swollen extremities, laboured breathing, ataxia, darkening of the skin and mucous membranes which disappeared one day post dose except at high dose levels. The colouration of tissues was attributed to the presence of iron.

Repeated dose toxicity studies revealed no deaths and no major adverse effects following administration for 28 days at a cumulative dose of approximately 192 and 108 times the intended human dose in the rats and the monkey respectively. Overt signs of toxicity were related to the large iron overload. These signs were not fully reversible after a 84 day treatment –free recovery period. These changes were not associated with histopathology. There were increases of ALAT and ASAT in both species without any associated histological lesions. These effects were of slight severity, only occurred at the high dose and with variability, especially in the rat. The values were stated to be within the historical control range. The applicant has hypothesised that this may be due to the accumulation of iron in the liver which may have induced some structural modifications of hepatocyte membranes for example by iron dependent increase in oxidative stress, leading to release of aminotransferases in the blood. This finding is not relevant to humans under the proposed clinical conditions of use.

Toxicokinetics evaluation was not conducted due to the i.v. route of administration and the proposed clinical single use. The pharmacokinetic parameters were determined at a clinical dose level, not covering the exposures in the toxicology studies. However, since Sinerem is slowly excreted, the repeated doses probably represent a higher dose level due to accumulation in the reticuloendothelial system. It is probable that the toxic effects were related not only to the plasma concentration of Sinerem, but to the accumulation of iron in the body.

A complete battery of *in vitro* and *in vivo* tests revealed that Sinerem was not genotoxic. Based on these results and the fact that Sinerem is intended for single dose clinical use only, no carcinogenicity studies were conducted and are not required.

Sinerem was without effect on reproductive performance and fertility of male and female rats and on early embryonic development of the F1 generation when administered before and during the first week of gestation. Nevertheless, when administered after the first week of gestation, Sinerem was maternotoxic, embryotoxic and teratogenic in both of the species tested, namely the rat and the rabbit. In view of the teratogenic effects, Sinerem will be contraindicated in pregnancy. Reproductive toxicity studies on pre- and post-natal development were therefore considered to be not necessary.

Local tolerance was satisfactory, only deposits of iron pigments were observed in the subepidermal tissue after perivenous or intra-arterial administration to rabbits. In addition, no sign of local irritation due to a direct effect of the product was observed in the monkey after repeated i.v. administration for 4 weeks.

Sinerem did not induce antigenicity in guinea pigs and mice and did not cause anaphylactic reaction in guinea pigs.

Sinerem is unlikely to pose an immediate risk to the environment.

A cardiovascular safety pharmacology study in monkeys was conducted in order to comply with current ICH requirements.

There were no major non-clinical concerns but there were 6 “other concerns”. These included concerns about pharmacodynamics, pharmacokinetics and toxicology. All these concerns have been satisfactorily answered and are considered resolved. The single exception was question 4, in which

there is the need for the applicant to accept an amendment to the wording in section 4.6 of the SPC. If this were to be accepted then this issue would be resolved. In summary, all the non-clinical concerns are considered to be resolved with the exception of question 4, which requires only the acceptance of an amendment to the wording in section 4.6 of the SPC.

III.3 Clinical aspects

Pharmacokinetics

The primary pharmacokinetics of Sinerem in man was derived mainly from one Phase I Study, supported by two other studies, one a Phase I Study and four subjects in a Phase II study.

The concentration of Sinerem in plasma was determined by measuring T1 and T2 relaxivity using a nuclear magnetic resonance spectrometer. The validation of the analysis method was meagre.

The distribution of Sinerem is limited to plasma water with a volume of distribution of about 3L. Clearance was very low, about 20 ml/day/kg. The mean half-life was estimated to be about 25 h. In the pharmacokinetic model used, the half-life was probably over-estimated and is likely to be somewhat lower than 25 h. Infusion rate, dose and gender do not seem to influence the pharmacokinetics of Sinerem. Pharmacokinetic studies were not performed in patients with impaired liver function. No pharmacokinetic drug interactions and the pharmacokinetic profile in renal-, cardiac or hepatic-impaired patient were performed. The applicant claimed that this was not considered necessary, since no major changes in the pharmacokinetics are foreseen.

There was no discussion regarding possible degradation of dextran in the circulation and if this could have implications on the cellular uptake of Sinerem.

The limited pharmacokinetic data is considered sufficient for this type of product.

Pharmacodynamics

The main interest is in Sinerem action on the MRI signal of target organs (mainly the liver and lymph nodes).

In healthy subjects: In total 4 pharmacodynamic studies were performed in 125 healthy subjects and have confirmed the signal decrease observed in normal lymph nodes, thus confirming the phagocytosis of nanoparticles by the macrophages of normal/inflammatory lymph nodes. The best imaging information are obtained on SET2 and GET2 from the 2.6 mg Fe/kg dose and were obtained 24 or 36 hours post injection of Sinerem, irrespective of the injection modality. The 2.6 mg dose was thus chosen for phase III studies.

No pharmacodynamic drug interaction study was performed and this is justified for a single-dose contrast agent like Sinerem.

In patients: The primary diagnostic efficacy endpoint was comparison of area under ROC (receiver operating characteristics) curves for plain and Sinerem MRI, on the patient or the lymph node group level, depending on the cancer type which is the most relevant one.

Trials were conducted to assess possible undesired pharmacological effects showed that Sinerem, has no effect on the QT/QTc interval and no immediate or delayed effect on immune function.

Clinical Efficacy

Dose-response studies and main clinical studies

Dose finding studies
The recommended effective dose (with maximum signal decrease was observed on T2-weighted sequences) for lymph node MRI for the pivotal and supportive studies was 2.6 mg Fe/kg. The choice of effective dose was based on observational data of subjective assessment and no statistical comparison was done on defined criteria.

Main Efficacy Studies
The current application is based mainly on one pivotal clinical study (ALS 44-003-A) and four supportive studies (ALS 3-7-A, ALS 3-35-A, 388 04-10, and ALS 3-33-A) on lymph node imaging in pelvis cancers.

The single Pivotal Study ALS 44-003A
A multi-centre (17), open-label trial comparing unenhanced MRI and Sinerem-enhanced MRI, using histology of the lymph nodes (LN) as the gold standard. A total of 271 patients presenting with a pelvic cancer (prostate, bladder, corpus or cervix uteri cancer) were enrolled in this study, of which 266 patients were analysed in the Full Analysis Set (defined as all included patients receiving at least one injection of contrast agent, regardless of the quantity injected).

The primary objective of this study was to compare the diagnostic performance of Sinerem-enhanced MRI versus unenhanced MRI at the patient level, in a population of patients for whom N-staging remained challenging (patients with large nodes excluded).

The primary efficacy variables were the sensitivity and specificity of MRI in assessing the nodal status (metastatic/non-metastatic) of the patient with respect to the LN concerned by lymphadenectomy.

The evaluations were performed by three independent off-site readers blind to the histopathological results. The readers were asked to read only lymph node areas corresponding to the lymphadenectomy specimen (lymphadenectomy area was marked on the images by an on-site radiologist). On-site reading of MR images was also performed and included as a secondary criterion for evaluation.

Pre-Sinerem MRI and pre+post-Sinerem MRI were compared using McNemars' test for the difference in sensitivity and the asymptotic 95% confidence interval was calculated for the difference in specificity; specificity of the two examinations were considered equivalent if the confidence interval's upper limit of pre+post-Sinerem MRI (respectively post-Sinerem MRI) specificity minus pre-Sinerem MRI specificity was greater than -5%.

A secondary comparison examines whether post-Sinerem MRI only (without reference to pre-Sinerem MRI) could be recommended and this may actually be of greater interest.

Discussion of Trial Results:

1. The pivotal study failed to demonstrate a consistent and statistically significant benefit for Sinerem in sensitivity and failed to confirm non-inferiority with regards specificity. Furthermore, the data generated in the single pivotal study are not consistent with those generated in the most relevant supporting studies (ALS 3 7 and 38804-10), where specificity seems to have been affected rather than sensitivity.

2. While there is some evidence for an increase in sensitivity, an important decrease in specificity cannot be ruled out and it is possible that the benefits of Sinerem differ for different locations of primary tumour.

3. The lack of consistency between the three readers, both with regards to initial assessment and post-Sinerem assessments (more concerning effect on specificity for reader 2) is worrisome.

4. The data on therapeutic strategies are of interest but are difficult to interpret as there is no absolute standard for this comparison. It was estimated that 13% of patients had therapeutic strategy changed based on the post-Sinerem MRI (compared to pre-Sinerem MRI). Whether the change was made for the better based on increased sensitivity or for worse based on decreased specificity remains unclear and is not resolved by the additional analyses presented.

Clinical studies in special populations

No pregnant women or children were included in the clinical trials with Sinerem, therefore the use of the Sinerem is not recommended in these groups.

Patients with hepatic and renal failure were included in the studies.

Analysis performed across trials (pooled analyses AND meta-analysis)

Studies have not been submitted.

Supportive studies

There were four supportive studies on lymph node imaging in pelvis cancers. Assessment of the supportive studies showed that Sinerem-enhanced MRI failed to demonstrate benefit compared with unenhanced MRI. It is considered that these studies provided little or no support to the pivotal study.

It is of note to mention here that 2 of the main supportive studies (ALS 3-7 and 388 04-10) were considered as non supportive of efficacy of Sinerem-enhanced MRI.

Clinical safety

Patient exposure

A total of 1,777 patients were enrolled in clinical studies, 1,663 of whom received Sinerem. 830 AE were observed with Sinerem *versus* 39 among the 75 patients with placebo.

Adverse events

Out of the 830 AE in the Sinerem group, 466 (56%) were rated as mild and 251 (30.2%) as moderate, and 96 (11.6%) as severe. Out of the 39 AE in the placebo group, 28 (71.8%) were rated as mild, 11 (28.2%) as moderate, and none as severe.

The differences in AE rates were not statistically significant with 50.0% in the Sinerem group and 52.0% in the placebo group.

The AE profiles as displayed by system organ class are similar, whether or not they are related to Sinerem.

More adverse events were experienced by patients who received Sinerem without prior dilution than those who received diluted Sinerem. The incidence rates and profiles of related adverse events were similar in the Sinerem and placebo group.

Adverse events were significantly more frequent in patients with a history of allergy.

In addition to the proposed target population of pelvic cancer patients the trials for Sinerem included patients with other types of cancer, and patients in other imaging studies. Only 21% of the patients in the clinical studies had pelvic cancer and received Sinerem for lymph node imaging. The company states that the adverse event profile was similar in the targeted and non-targeted indication populations.

The most commonly reported AE in the Sinerem group was back pain. 86.3% of events were mild to moderate, and 50% began within the first 5 minutes after administration and resolved before the end of the infusion. The majority of the first observed symptoms consisted of hypersensitivity reactions (merging pruritus, urticaria, rash and erythema). These symptoms usually occurred rapidly, during infusion, and led to temporary or definitive discontinuation of the infusion in a number of cases. Other symptoms are “flushing” and “feeling hot”, and considered as non-allergic and “infusion-related reactions”.

The incidence of “chest pain” was low and similar between the Sinerem group (1.4%) and the placebo group (1.3%). The incidence of “hypotension” or “blood pressure decrease” was very low: 12 AE (0.7%), of which 3 were serious.

Serious adverse events and deaths

Out of a total of 1663 patients, 12 (0.72%) patients in the Sinerem group died. Only one death was considered to be related to the administration of Sinerem. This death was in study 38804-8A and was due to an anaphylactic shock (onset two minutes after the direct injection of the undiluted product at a rate of 2 ml/min). The patient had liver suspected metastasis (metastatic cancer of the colon treated by chemotherapy), known history of allergy to iodinated contrast agent and hypertensive treated by three different drugs. The Study 38804-8A, was a phase III safety and efficacy study in 125 patients or placebo.

Of the 44 patients who experienced a serious adverse event, 7 were considered related to Sinerem (an estimated risk of between 0.2% and 0.9%) including the fatal case. No SAE were reported in the placebo group.

In the pivotal study (ALS 44-003) there were three deaths and all were deemed by the investigator as unrelated to Sinerem.

Laboratory findings

Iron metabolism: Significant and reversible modifications in laboratory parameters related to iron metabolism were observed after administration of Sinerem. Mean values for serum iron, total iron binding capacity, and percent saturation increased within the 24-hour period following administration of Sinerem and then decreased to or below baseline levels by day 7. The values remained fairly constant thereafter. Serum ferritin levels peaked in a dose-dependent fashion at day 3 after administration of Sinerem and remained elevated at day 7. The mean values remained elevated for 5 months in the 2.6 mg Fe/kg group. These changes reflect the incorporation of metabolised Sinerem into total body iron stores. No subjects had any adverse events or other safety problems related to these changes. Moreover it must be noted that the dose of Sinerem (182 mg Fe for a 70 kg person) is less than the iron contained in a single unit of blood (200 mg) and small in comparison to normal total body iron (about 3,500 mg).

Sinerem produced no consistent, clinically significant effects on blood chemistry, hepatic function, electrolytes, ancillary tests and haematology tests. Sinerem does not induce any consistent clinically significant effects on urea and creatinine levels. The changes that occurred were attributed to the subjects’ primary diseases or underlying conditions such as diabetes, concomitant therapies, or pre-existing laboratory abnormalities.

Safety in special populations

No pregnant women or children were included in the clinical trials with Sinerem, therefore its use is not recommended in these groups.

Sinerem can be used in elderly patients with no particular additional recommendations.

Sinerem was used in a small number of patients with a history of cirrhosis or multiple sclerosis; with an increase in the AE rate observed in such patients.

Immunological events

In a study in healthy subjects demonstrate that administration of a single 1.1 or 2.6 mg Fe/kg dose of Sinerem has no immediate or delayed effect on immune function.

Safety related to drug-drug interactions and other interactions

No pharmacodynamic drug interaction study was performed and this is justified for a single-dose contrast agent like Sinerem.

Discontinuation due to AES

Hypersensitivity reactions (merging pruritus, urticaria, rash and erythema) symptoms which usually occurred very rapidly, during infusion, had led to temporary or definitive discontinuation of the infusion in a number of cases.

Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management plan

Training programme for all potential users of Sinerem- this will be a User's guide or DVD. Formal training sessions will be organised in centres of excellence for users of Sinerem. These will cover administration and identified and potential safety risks with Sinerem.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

No new clinical trial data are presented. The existing clinical trial data have been further explored in an attempt to address the outstanding concerns.

The Applicant argues that some of the pivotal trial data should be disregarded as the readers have performed poorly. They argue that when these data are disregarded, the trial results indicate a favourable risk/benefit balance. Exclusion of trial data is not accepted however. A heterogenous mix of readers and a certain amount of between-reader variability is considered reflective of clinical practice. Improved diagnostic capability should be demonstrated in such circumstances. As it is, evidence of improved diagnostic capability remains weak from the pivotal study and inconsistent

with the supporting studies. Only limited data are provided in comparison to CT and none in comparison to PET. It is possible that this might not preclude a positive opinion were the benefit/risk clearly favourable. However, it is presently considered that none of the major objections are resolved. Thirty-two out of the 42 of the clinical other concerns questions are resolved. However, issues remain over the potential for information carryover and with regards the precise clinical use of the product, which appears not to reflect the clinical trial.

The CHMP considers the risk/benefit unfavourable at this stage.

V.1 Conclusions

Despite the lack of any major safety concern other than one death from anaphylaxis with the direct injection of the undiluted contrast, the efficacy data are too weak to indicate a positive risk/benefit balance.

No additional comments were received in relation to Quality following circulation of the D150 joint report.