SCIENTIFIC DISCUSSION

1. Introduction

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) has proved to be an extremely valuable diagnostic imaging modality since its introduction as a clinical tool in the 1980s. MRI has provided several benefits over previously existing diagnostic imaging modalities. These advantages include multiplanar capabilities (axial, coronal, and sagittal sections), no exposure to ionizing radiation, visualization of contrast resolution between various tissues and the determination of several intrinsic tissue characteristics (T1, T2, and proton density). Large lesions may be detected with MRI without a contrast agent; however, the detection of small lesions such as early brain metastases or small liver metastases requires high lesion contrast.
The magnitude of signal detected and displayed in MRI is dependent upon the imaging pulse sequence (a set of variables controlled by the Radiologist), and several intrinsic tissue characteristics. These intrinsic tissue characteristics include the proton density (PD) and proton T1 (spin-lattice) and T2 (spin-spin) relaxation times.
The potency of a contrast agent is determined by measuring its effect on the relaxation rate (1/T1), which is the inverse of the relaxation time. Larger 1/T1 values translate into larger signal intensities. In vitro 1/T1 is directly proportional to the concentration of the contrast agent in a solution or a tissue sample. The relaxivity of a contrast agent is this experimentally determined proportionality constant, and the larger the relaxivity of a contrast agent, the larger the increase in signal intensity for a given concentration of the agent.

The enhancement of brain tumours using a gadolinium (or Iodine) containing contrast agent depends on the disruption of the blood brain barrier (BBB). As a result, these agents have been referred to as markers for sites of abnormal BBB breakdown. When the BBB is disrupted, the gadolinium molecules diffuse into the interstitial compartment thereby producing the characteristic paramagnetic effect of T1 and T2 shortening. In general, the addition of contrast to MRI, at the standard clinical dose of 0.1 mmol/kg, has led to a significantly improved lesion detection, definition and specificity as compared to CECT.

Concerning the detection of liver lesions the hepatic artery and portal venous system supply approximately 20% and 80% of the hepatic blood supply, respectively. The earlier (hepatic arterial phase) images provide optimal lesion conspicuity for hypervascular lesions and the portal venous phase images are useful for hypovascular lesions. Typical hepatic imaging protocols are designed to include a series of imaging sequences with the understanding that some lesions will be detected more readily during the hepatic arterial phase, some during the portal venous phase and some during the equilibrium phase of contrast enhancement.

About the product

OptiMARK is a gadolinium–containing MRI contrast agent to induce signal intensity changes within a lesion, thereby facilitating its recognition from the surrounding normal structures. This is done by the use of the metal gadolinium, which due to its atomic structure, acts indirectly on the local magnetic environment to alter proton T1 relaxation times.

Gadoversetamide is similar in structure to the active substance in the Magnevist formulation (gadopentetate dimeglumine). Both OptiMARK and Magnevist, extracellular gadolinium chelates, have similar biodistribution and elimination characteristics when compared to each other and to iodine contrast agents like those used during contrast enhanced computed tomography (CECT). Therefore, a significant portion of both the Nonclinical and Clinical Pharmacology program was designed to explore the relaxivity and pharmacokinetics of OptiMARK and to compare them to those of previously approved MRI contrast agents such as Magnevist.

A marketing authorisation application for OptiMARK was submitted in 1998 and was withdrawn in 1999 following an oral explanation in front of the CPMP due to the fact that some outstanding clinical and biostatistical questions could not be satisfactorily resolved. Based on a CHMP scientific advice received in May 2005 a complete re-read of the magnetic resonance images which formed the basis for the pivotal phase 3 study results was undertaken by an independent consulting firm.
OptiMARK was approved by the Food and Drug Administration (FDA) in 1999 and subsequently in 15 countries over the world. In the countries where it is registered, OptiMARK is used with MRI in patients suspected of abnormal blood brain barrier breakdown or abnormal vascularity of the brain, spine and associated tissues. OptiMARK is also used with MRI to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver of patients highly suspected of liver structural abnormalities.

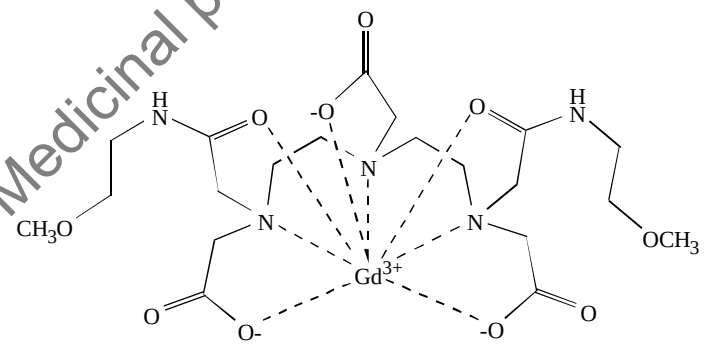
2. Quality aspects

Introduction

OptiMARK is a clear, colourless to slightly yellow solution for injection, containing 0.5 mmol/ml of gadoversetamide, in a formulation also containing the novel excipient versetamide as a stabiliser. OptiMARK is a novel contrast medium for magnetic resonance imaging. Gadoversetamide is a chelate of gadolinium and the ligand versetamide, and is structurally related to the existing contrast media gadopentetate dimeglumine ('Magnevist') and gadodiamide ('Omniscan').
It is supplied in glass vials and in polypropylene pre-filled syringes. The concentration of 0.5 mmol/ml is appropriate in view of the intended dosage of 0.1 mmol per kg of body weight, administered as a bolus i.v. injection.
OptiMARK was the subject of a centralised application in 1998, which was subsequently withdrawn.

Active Substance

Gadoversetamide is the recommended INN for the complex of Gd^{3+} and a novel ligand, versetamide (recommended INN), which is a derivative of the chelating agent diethylenetriamine pentaacetic acid (DTPA**)**. The Gd^{3+} ion is bonded to three nitrogens on the diethylenetriamine backbone, to three carboxylate oxygens and to two carboxamide oxygens, as is shown in the figure below:



The molecular formula is $C_{20}H_{34}N_5O_{10}Gd$ and the molecular weight is 661.8.
Gadoversetamide's Generic Name is Gd-DTPA- bis (methoxyethylamide) and is structurally related to gadopentetate dimeglumine (Gd-DTPA dimeglumine) and to gadodiamide (Gd-DTPA-bismethylamide) – agents that are currently widely used as contrast media for magnetic resonance imaging. It is hygroscopic and highly soluble in water (~1.2 g/ml). In relation to its diagnostic function, its molar relaxivity in water is 4.3 $mM^{-1}S^{-1}$, a value similar to gadopentate. The butanol:buffer partition coefficient (log P) was determined to be -1.82. Two polymorphs were identified using X-Ray diffraction, however both are equally soluble and IR and NMRD spectroscopy demonstrate that they are equivalent in solution. Because OptiMARK is a dilute solution the existence of two polymorphs is of no practical significance for the product.

- Manufacture

The manufacture involves a three-stage synthesis and one purification step and has been satisfactorily described. In the whole process no catalysts used. Several reprocessing steps have been laid down. In these steps no other materials are used than in the main process. The specifications for all reagents and solvents are considered to be satisfactory. In-process controls are specified for each step in the process and are considered to be acceptable.

- Specification

The specification for the control of the active substance includes tests for appearance, colour (UV), identification (HPLC, Colorimetric test), assay of gadoversetamide (HPLC) and free gadolinium (III) and total chelating material (titration), Water, (Karl-Fischer), residual solvents (GC), heavy metals (Ph. Eur.), endotoxin (LAL), total viable aerobic count (Ph. Eur.) and related substances (HPLC). Three different HPLC methods are used for the determination of impurities and degradation products depending on the nature of each one of them. All impurities were qualified with relevant toxicological studies.

- Stability

Stability results have been provided for three commercial-scale batches of gadoversetamide packaged in the commercial packaging. A long-term study is being conducted at 25 ºC/60% RH and will continue for 36 months. A study under accelerated conditions was conducted at 40 ºC/75% RH for six months.

Results have been provided for 24 months under long-term conditions and for six months under the accelerated conditions. All batches fully complied with the specification at all test points. Apart from an increase in water content, no clear trends emerge from a review of the stability data and, therefore, the proposed retest period is accepted.

Additionally, a report of forced degradation studies conducted using samples of gadoversetamide was submitted. The results of the study indicate that the stability of the active substance is only significantly affected, when heated in aqueous solution at pH 9.0, with degradation to form two specified impurities.

Photostability testing has not been performed on the active substance, however it is accepted that the proposed container sufficiently protects the active substance from UV light during storage. In addition, OptiMARK medicinal product, which consists of the active substance and the ligand versetamide in water, was found to have limited photosensitivity in stability testing, and therefore it can be safely assumed that the active substance and ligand should have limited photosensitivity as well.

Finally, no impact of gadoversetamide polymorphism on the thermodynamic stability was observed.

In conclusion, on the basis of the submitted stability data, as discussed above, the claimed re-test period and storage condition can be granted.

Medicinal Product

- Pharmaceutical Development

OptiMARK is a sterile injectable solution intended for intravenous administration. The concentration of 0.5 mmol/ml was chosen to facilitate the administration of the standard clinical dose for MRI contrast media. The osmolality is approximately 3.9 times that of plasma, which is similar to that of other agents in the class. Nevertheless, the overall safety of OptiMARK, established in nonclinical and clinical models suggests that a bolus dose of maximum 1-2 ml/min of a 500 micromol/ml dose would be sufficiently diluted in the blood ensuring that any potential safety issues associated with the hypertonicity would not occur. Furthermore, the viscosity is appropriate for a small volume injection at the anticipated human dose and the pH of the solution is close to physiological values. Product stability was found to be optimum at pH < 6.8 and it is adjusted with sodium hydroxide or hydrochloric acid. It has been found that the product is stable at elevated temperatures provided the initial pH value was less than 6.8.

Other studies showed that the stability of the product is not affected by exposure to air or oxygen, however, as an additional precaution, the product is filled under nitrogen. It was found that the impact of the tested buffers did not improve significantly the stability profile of the formulation so they were omitted from the final formulation. In addition, since the product is a solution and the active substance

is very soluble in water, the polymorphic form, particle size distribution and surface area of the later do not affect the bioavailability and/or the stability of finished product.
The active substance is a complex of gadolinium and versetamide, which is a novel excipient. The active substance and the new excipient are manufactured largely in the same way and only the last step of the synthesis differs. Satisfactory data on the manufacturing, control, stability and toxicology of this new excipient have been submitted.
Appropriate studies were done with regard to stabilising the gadoversetamide complex, and the most suitable counter-ion for the free versetamide. The molar ratios of versetamide and calcium were chosen based on appropriate toxicity studies. Finally, holding times, filtration and sterilisation have been identified as critical process steps. Individual studies were conducted to validate them and have been satisfactorily validated.

- Adventitious Agents

No excipients of human or animal origin are used in the manufacture of OptiMARK.

- Manufacture of the Product

The manufacturing process involves several steps of dissolution of the drug substance and excipients in water for injections while adjusting the pH of the solution to the desired levels. Vials are filled and concurrently purged with nitrogen, capped and sterilised by autoclaving. Syringe barrels are washed, siliconised and filled, then the pistons are fitted onto the filled barrels and the syringes are sterilised by autoclaving. The sterilisation occurs at standard Ph. Eur. conditions.

- Product Specification

The specification for OptiMARK includes tests for appearance, odour, colour (UV), pH (potentiometric), identification (HPLC, colorimetric test), assay of gadoversetamide (HPLC), free and total gadolinium (UV), total chelating material (titration) and calcium (atomic absorption), specific gravity (density meter), osmolality (vapour pressure lowering apparatus), particulates (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), extractable volume (only for vials, volumetric cylinder), syringe function tests (in-house force gauge) and related substances (HPLC). Three different HPLC methods are used for the determination of impurities and degradation products depending on the nature of each one of them.
The tests and limits of the specifications for OptiMARK solution for injection are appropriate to control the quality of the finished product for the intended purpose.

- Stability of the Product

Glass vials: Three batches per vial volume (12 batches in total) were stored long term, under 30 °C/60 % RH for 12 months, and under accelerated conditions at 40°C/75 % RH for 6 months, in both the upright and inverted positions. The long-term conditions are more severe (30 rather than 25 °C) than those envisaged in the current stability guidelines, but this is acceptable as it will tend to produce a more conservative estimate of the shelf-life. In addition, stability samples were tested for container closure integrity using a dye bath.
Polypropylene syringes: Three batches per vial volume (12 batches in total) were stored long-term under 25 °C/40% RH for 36 months and under accelerated conditions at 40 °C/20% RH for 6 months; all samples were stored in a sideways orientation. The temperatures used comply with current stability guidelines, but the relative humidity was considerably lower than the guidelines' recommendations. In the case of an aqueous solution supplied in a plastic container, low ambient humidity would increase the rate of vapour transmission, while high ambient humidity would not compromise product stability. The conditions used in the trial would therefore tend to shorten the shelf-life.
In addition, stability samples were tested for vapour transmission, for container closure integrity using a dye bath and for extraction of additives from the polypropylene syringe.
The container/closure integrity of the syringes was also tested after freeze-thawing. It was found that the integrity of the closure was compromised in samples that had been frozen and thawed. In addition samples of OptiMARK were stored at 60°C for 14 days. No evidence of instability was observed during this period.

Results for both vials and syringes at all the different conditions and for all batches were found to comply with the product specification at all test points.

Photostability was investigated for both vials and syringes by exposing one batch of each packaging material under a xenon light source to 1.2 million lux hours. Results revealed an increase in the content of unspecified impurities and a slight increase in pH, indicating that the product should be protected from light.

In addition, four batches of each packaging material were subjected to double autoclaving but no significant differences were observed between the product samples that were single- and double-autoclaved.
Based on the overall stability data, the proposed shelf-life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects
The quality of OptiMARK solution for injection is adequately established. In general, sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the active substance and medicinal product has been presented. Satisfactory data have been provided in support of the novel excipient used in the finished product.
There are no major deviations from EU and ICH requirements. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics. Stability tests indicate that the product is chemically stable for the proposed shelf life.
At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit-risk balance of the product. The applicant committed to resolve these as Follow-Up Measures after the opinion, within an agreed timeframe.

3. Non-clinical aspects

Introduction

All pivotal studies were conducted according to GLP. The studies conducted were sufficient in number and type, contained adequate group sizes to assess the toxicological effects of gadoversetamide in laboratory animals and permitted determination of the drug's safety in humans.

Pharmacology

OptiMARK has a similar structure, although chemically distinct, to an already marketed gadolinium chelate product, Magnevist. Primary pharmacodynamic studies focused on comparisons of the ability of OptiMARK and Magnevist to alter proton relaxation times in vitro and in vivo.

- Primary pharmacodynamics

The main in vitro study tested the equivalency of OptiMARK and Magnevist in terms of ability to alter T1 and T2 relaxation times in water and in 4% BSA using a Bruker NMR Minispec PC120 (20 MHz, 0.47T). In each solution, for two concentrations (0.25 to 10 mM), the agents had similar relaxivity values, R, both in value and in gradient. In all cases, R for OptiMARK was statistically significantly more relaxive than Magnevist.

Table 1: Effects on Proton Relaxivity

	R_1 ($mM^{-1}sec^{-1}$)		R_2 ($mM^{-1}sec^{-1}$)	
Test Article	**Water**	**BSA**	**Water**	**BSA**
OptiMARK	4.4*	4.5*	4.9*	5.2*
Magnevist	3.8	4.2	4.3	4.8

*Value significantly greater than corresponding measurement with Magnevist ($p<0.001$)

Difference between phantom samples of OptiMARK and Magnevist were also tested. 16 sealed samples ranging in concentrations from 1 microM to 10 mM were placed upright in a Styrofoam

container within the headcoil of either a whole body scanner (1.5T) or an animal scanner (4.7T). For each scanner, a single coronal slice was taken (TR-500 ms, TE = 20 ms) which yielded an image containing 16 circles representing the 16 solutions. Signal intensities were plotted as a function of the concentration of each agent, reaching a maximum intensity at 1 mM, where after the signal decreased. Resulting curves were nearly identical, supporting the evidence that the imaging properties of OptiMARK and Magnevist are equivalent.

In vivo the renal contrast enhancement of OptiMARK versus Magnevist was evaluated in a 7-day crossover direct comparison study in rabbits. Contrast was injected into anaesthetised male New Zealand rabbits via i.v. ear drip as a bolus agent (0.1 mmol/kg) followed by a 6 ml flush of saline. Rabbits were imaged with a 4.7 T/440 animal scanner and phantom samples were measured. Images were taken pre and post injection using similar specifications and TS= 300 ms, TE = 18 ms. A second imaging was performed one week later. The signal intensity was greatest at 5 minutes post injection, gradually decreasing over the 90 minutes. For qualitative assessment, films from the 20 min post-contrast image were prepared and compared by two blinded radiologists. Based on both quantitative and qualitative data from the study time intensity curves were similar for each agent and there were no appreciable differences in the imaging effects of OptiMARK and Magnevist.

And additional study was performed in an experimental model of cerebral metastatic disease. Twenty male New Zealand rabbits were injected intracerebrally with 1 million VX2 carcinoma (adenocarcinoma) cells suspended in 0.1 ml buffered saline. At 10-14 days post injection, the animals were imaged twice with a 24-hour delay between scans. For the first image, the animals received OptiMARK bolus 0.3, 0.4 or 0.5 mmol/kg i.v. In the second image, the animals received 0.05, 0.2 or 0.1 mmol/kg respectively. There were 5-6 animals per dose pair. In addition, 5 animals received either 0.1 mmol/kg of OptiMARK or 0.1 mmol/kg Magnevist. Imaging was performed on a 1.5T scanner and parameter specifications for both scans were identical. The presence and extent of tumours were compared with T1 weighted pre and post contrast spin echo scans and T2 weighted scans. Contrast enhancement values (CEV) were calculated for each tumour. For concentrations of 0.05 to 0.4 mmol/kg, there was an increase in CEV intensity with a plateau at > 0.4 mmol/kg. 0.05 mmol/kg doses were able to identify 50% of what 0.3 mmol/kg could identify. 0.1 mmol/kg was able to identify 71% of what 0.5 mmol/kg could identify. At 0.2 mmol/kg, it was possible to identify all tumours seen with the 0.4 mmol/kg doses. OptiMARK was shown to be equivalent to Magnevist at equivalent doses (same number of tumours seen in the same animals).

To address OptiMARK permeability to the Blood Brain Barrier (BBB) 12 New Zealand rabbits were injected with VX2 carcinoma cells into their brains, and 10-14 days later, MRI studies were performed using a bolus i.v. dose of OptiMARK (0.3 – 0.5 mmol/kg). A 1.5T clinical scanner was used and T1 weighted scans were conducted pre-contrast injection and every minute for 15 minutes post injection. A comparison was made between the MRI images and microscopic histopathological findings. Analysis was made on the basis of blinded and non-blinded interpretation. Using T1 weighted imaging scanning, OptiMARK was able to identify experimental cerebral tumours as small as 0.6 mm^2 in size. T2W MRI identified only 20 of 104 tumours and therefore the authors considered that this imaging method was poor for diagnosis of cerebral tumours. OptiMARK and Magnevist have comparable performance in detecting experimental metastatic disease at 0.1 mmol/kg.

- Secondary pharmacodynamics

A general pharmacology study including both in vivo and in vitro tests investigated the comparative effects of OptiMARK and Magnevist on general signs and symptoms, CNS, smooth muscle, digestive system, somatic nervous system and renal function. The doses used were: 0.5 mmol/kg, 1.5 mmol/kg, and 5 mmol/kg i.v. of OptiMARK or Magnevist. OptiMARK showed some CNS activity, but only at the highest dose (50 times higher than clinical doses) and for some responses such as on body temperature, convulsions or analgesia no effect was noted. There were no effects on the digestive, renal and somatic nervous system. High doses of Magnevist caused some renal, smooth muscle and somatic nervous system effects, however none of these effects are considered to be a concern at clinically relevant doses.

Additional studies at clinically relevant concentrations of OptiMARK show that there are no respiratory, CVS, CNS, smooth muscle or renal system effects. All the studies performed are summarized in the following table:

Study Number	**Aim**	**Strain of Animals / Number of animals / Sex**	**Agonist name and dose**	**Results with OptiMARK**	**Results with Magnevist**
1101/05/93/027-E*	Effect on histamine-induced contraction of guinea pig trachea	Hartley Guinea Pigs/ 4 tissues per group/ Male	Histamine 2 microM	15mM: 49% reduction in the contractile response elicited by histamine	15 mM: 78% reduction in the contractile response elicited by histamine
1101/05/93/028-E$	Effect on histamine and acetylcholine induced contraction of guinea pig trachea	Hartley Guinea Pigs / 4 tissues per test article concentration / male	Histamine 2 microM Acetylcholine 5 microM	Reduction in the contractile response elicited by histamine: 1.5mM: 9% 5 mM: 13% 15 mM: 45% ($p<0.05$) Reduction in the contractile response elicited by acetylcholine: 1.5 mM: 7% ($p<0.05$) 5 mM: 27% ($p<0.05$) 15 mM: 44% ($p<0.05$)	Reduction in the contractile response elicited by histamine: 1.5 mM: 7% 5 mM: 19% ($p<0.05$) 15 mM: 46% ($p<0.05$) Reduction in the contractile response elicited by acetylcholine: 1.5 mM: 7% ($p<0.05$) 5 mM: 16% ($p<0.05$) 15 mM: 36% ($p<0.05$)
1101/05/93/029-E	Effect on norepinephrine induced contraction of isolated rat aorta	Sprague Dawley Rats / 4 tissues per test article concentration / male	Norepinephrine 6 microM	Reduction in contractile response elicited by norepinephrine: 1.5 mM: no response 5 mM: no response 15 mM: 3%	Reduction in contractile response elicited by norepinephrine: 1.5 mM: no response 5 mM: no response 15 mM: 6%

*Study 1101/05/93/027-E: OptiMARK versus Magnevist: Effect on histamine induced contraction of guinea pig trachea. Isolated tracheas were treated with histamine 2 microM and allowed to reach equilibrium, and then 0.9% (900 microl/bath) saline was added to the bath. Following a 30-minute wash period, three further contractions were elicited with 2 microM histamine. Then the tissues were retreated with histamine 2 microM, and after equilibrium was reached, tissues were treated with either 15 mM OptiMARK or Magnevist. Saline resulted in a 5% and 9% reduction of the contractile response induced by histamine in the two tested groups of tracheas (one for OptiMARK and one for Magnevist)

$Study 1101/05/93/028-E: methodology was almost identical to study 1101/05/93/027-E. Whereas histamine alone was used as an agonist in the previous study, the tissue samples in this study were also stimulated with acetylcholine. 0.9% saline was added at either 90, 300, 900 microl/bath in study 1101/05/93/028-E and did not produce any significant reductions in histamine or acetylcholine contractile response.

Study 1101/05/93/029-E: 0.9% saline added at either 90, 300, or 900 microl/bath produced statistically significant ($p<0.05$) increases in contractility of rat aorta that was not considered biologically relevant. The reduction of contractile response noted at high doses of contrast agents were not considered biologically relevant.

- Safety pharmacology programme

The potential of OptiMARK to prolong QT intervals was assessed by examining its effects on the cardiac action potential of an appropriate *in-vitro* test system such as isolated Purkinje fibres from the beagle dog. The effects of OptiMARK were compared to those of the commercially available magnetic resonance contrast agents Magnevist, Omniscan and ProHance and to gadolinium chloride. The contrast agents were studied at concentrations of 2.5, 7.5, 25, 75 and 250 micromol/ml (2.5-250 mM) with an exposure time of 30 minutes (6 fibres per each test). Gadolinium chloride was tested at 1, 3, 10, 30 and 100 µM concentrations. OptiMARK, Omniscan and ProHance all produced significant prolongation of APD_{60} (96.3% $p<0.0005$) and APD_{90} (81.6%, $p<0.0005$) at the highest concentration, 250 micromol/ml, which was at least 100x the maximum plasma concentration that would be achieved under conditions of clinical use. Purkinje fibres treated with Magnevist at the highest concentration, 250 micromol/ml, were unable to generate action potentials. At 75 micromol/ml, Magnevist caused a reduction in UA and MRD. Gadolinium chloride had little effect on the cardiac action potential.

In vivo safety pharmacology studies were performed to investigate potential effects of OptiMARK prolonging the QT interval as well as its effect on other cardiovascular parameters using dogs. Animals were anaesthetized, had their sino-atrial nodes destroyed and the heart artificially paced. Test drugs were injected into the femoral vein and then flushed with 5 ml saline. A 30 min time lapsed between successive doses. Measurements of cardiovascular parameters were made at 15, 30, 60, 120, 240 sec and longer after injection. In all the studies, the findings showed that there was no QT prolongation potential of OptiMARK at the doses tested which were as high as 20x the clinical dose (on BW basis) and 10x (on BSA basis) of 0.1 mmol/kg. The rate of administration did not influence these results.
One further study evaluated OptiMARK in conscious telemetered dogs. This study also noted that OptiMARK should be unlikely to have effects on QTc and other parameters at the clinical dose.

- Pharmacodynamic drug interactions

No studies available.

Pharmacokinetics

Absorption, biodistribution, metabolism and excretion of OptiMARK were studied in rats and dogs, the two species in which principal toxicology studies were conducted. Special studies included a study of the secretion in milk of lactating female rats, biodistribution in maternal and foetal tissues after administration to pregnant rats and a study of biodistribution and excretion in anephric rats.

Analytical methods used in these studies included a gadoversetamide-specific reverse phase chromatographic assay, detection of Gd^{153} from radiolabelled gadoversetamide in OptiMARK (a gamma emitter readily detected by gamma scintillation counters) and an assay of gadolinium by inductively coupled plasma atomic emission spectrometry (ICP-AES) and inductively coupled plasma mass spectrometry (ICP-MS).

- Absorption

A series of studies were carried out to determine some pharmacokinetic parameters for gadoversetamide (see table below). In the first study rats (SD) received dose of 0.03-0.10-1.0 mmol/kg iv Gd^{153}-labelled gadoversetamide, followed by serial plasma sampling. Additional groups of rats received 0.10 mmol/kg iv. In two separate studies male dogs received 0.1 mmol/kg iv Gd^{153}-labelled gadoversetamide and female dogs received 0.1-0.9 mmol/kg iv Gd^{153}-labelled gadoversetamide. Serial samples of blood, urine, faeces and tissues were taken. The volume of distribution (Vd) was equivalent to the extra-cellular fluid space and the clearance (Cl) was equivalent to the glomerular filtration rate in dogs.

Pharmacokinetic parameters following a single i.v. dose of gadoversetamide (plasma data)

Study	Species	Sex	Dose mmol/kg	Cmax geq/g	Tmax h	T ½ h	AUC_{0-48hr} geq.h/g	Vd L/kg	Cl L/kg/h
Oread 5059	Rat	M	0.03 iv	35	0.083	0.36	24		
(preliminary			0.1 iv	247	0.083	0.32	154		
study)			1.0 iv	1295	0.083	0.32	748		
Oread 5059	Rat	M	0.1 iv	220	0.083	0.30	129		
(main study)		F	0.1 iv	194	0.083	0.34	127		
Oread 5057	Dog	M	0.1 iv	277.0	0.083	0.67	222*		
1101/05/92/	Dog	F	0.1 iv			0.74		0.22	0.21
007			0.9 iv			0.88		0.31	0.25
1102/04/003	Dog**	M,	0.1 iv			0.65	64	0.25	0.26
Wible and		F	0.3 iv			0.82	176	0.32	0.27
Hynes *(New*			1.0 iv			0.74	658	0.26	0.24
data)			3.0 iv			0.77	2039	0.26	0.24

* - $AUC_{0-\infty}$

** serum data

The labelled gadoversetamide distributes in the plasma but doesn't enter RBC, 90-93% is excreted in the urine with negligible amounts found in other tissues.

- Distribution

An organ distribution assay was conducted using Gd^{153} radiolabelled OptiMARK. Twelve SD rats were dosed with 0.1 mmol/kg OptiMARK and 12 SD rats were dosed with 0.9 mmol/kg OptiMARK. Faeces and urine were also collected for examination. Greatest radioactivity was found 0.5 hours after dosing (1-8%) in the kidney and in organs making up the most of body mass (blood, muscle, skin, skeleton). Radioactivity declined rapidly and 24 hours after dosing, less than 1% of the original dose remained in any organs. After 48 hours, 0.25% of the radioactivity still remained in the skeleton. Most of the radioactivity appeared in the urine. In conclusion, OptiMARK is rapidly excreted primarily via the urine without selective organ retention.

T1 and T2 relaxation times were measured in serum, muscle and kidney of 12 male SD rats with 0.1 mmol/kg OptiMARK. Another group of twelve rats was treated with the same dose of Magnevist. These values (with Gd concentrations) were used to calculate tissue relaxivities (R1 and R2). There was no difference in biodistribution, half-life and volume of distribution or clearance between OptiMARK and Magnevist. Similar R1 and R2 values suggested that imaging capability *in-vivo* is comparable.

Two additional 7-day biodistribution studies were conducted in male rats. Gd^{153} was rapidly cleared from blood, liver, spleen, kidneys and bone. At 24 hours, no radioactivity was found in blood with 0.5-0.7% of the injected dose in the kidney, <0.3% of the injected dose in bone and liver, and ~0.005% of the dose in spleen. Thereafter, radioactivity continued to decline through the 7-day period

in kidneys, liver and spleen, but remained relatively constant in bone at ~0.2-0.3% of the injected dose.

Biodistribution was also studied in female beagle dogs. Four dogs were administered with either 0.1 mmol/kg i.v. or 0.9 mmol/kg i.v. Elimination half-life was between 0.736 and 0.878 hours. Volume of distribution was 22-31% of body weight and clearance was 0.208-0.254 l/kg/hr (similar to the glomerular filtration rate in the dogs). Recovery of 92-94% of dose was found in the faeces and urine (predominantly urine). Less than 1% radioactivity remained in organs after 48 hours of dosing.

In pregnant/lactating rats the concentration of Gd^{153} in the placenta/amnion reaches 0.4-times the maternal plasma Tmax, but takes longer to clear, it was still detectable at 24 hr. As a percentage of dose, exposure peaks at 1.95%, 0.7% at 24 hr. Exposure of the foetus is negligible, 0.013-times maternal or 0.25% of dose. Gadoversetamide is secreted in the milk; Tmax = 1 hr, Cmax = 10.98 gee./ml, still detectable at 24 hr. The milk:plasma ratio increases with time, 0.5-3 hr, due to faster excretion from plasma, 0.14-3.64% of dose.

In vitro studies using human, dog and rat plasma demonstrated that OptiMARK does not bind to plasma proteins. Binding ranged from –1.96 to 2.36% in the three species tested with concentrations of 0.33 mM and 3.33 mM OptiMARK. These concentrations represent an estimate of the concentration that will be present in plasma after 0.1 mmol/kg (clinical dose) and 0.9 mmol/kg administrations.

- Metabolism

The metabolism of OptiMARK was analyzed in several *in vivo* studies.
Study 1: Male rats were treated with a dose of 0.9 mmol/kg of Gd^{153} labelled drug. 24-hour urine collections were assayed for radioactivity and also subjected to liquid chromatographic assay of gadoversetamide. In both assays all of the Gd^{153} was in the form of the active substance gadoversetamide. No spurious peaks were seen in the chromatographic assay. These results show no evidence of metabolism of gadoversetamide.

Study 2: A rat study examined plasma and urine for metabolites after a dose of 0.1 mmol/kg OptiMARK using liquid chromatographic assay. Plasma levels of gadoversetamide decreased from ~0.2 mg/ml, at 5 minutes post-injection, to less than detectable (<0.002 mg/ml) at 2 hours post-injection. Twenty-four hour urine collections contained 0.5-0.7 mg/ml of gadoversetamide. Small chromatographic peaks, estimated to be about 0.002-0.008 mg/ml, and seen at the solvent front in both plasma and urine samples, were later determined to be artefacts of the analytical method.

Study 3: This rat study investigated the metabolic fate and protein binding of Gd^{153} OptiMARK in plasma, urine, bile, faeces, liver, testes and bone. No metabolism was detected in any tissue or excreta specimen. Binding to plasma protein was nil at 15 minutes and minimal (~1.0%) at 45 minutes. Little protein binding was found in urine, bile or faeces. Protein binding was greatest in liver and testicular specimens (27% of liver radioactivity and 33% of testicular radioactivity at 45 minutes).

Study 4: The metabolism of gadoversetamide was studied in plasma and urine of female dogs after a 0.1 mmol/kg dose of OptiMARK using liquid chromatography. Plasma samples were obtained at 2, 5, 15, 30, and 45 minutes, and at 1, 1.5, 2, 3, 4 and 8 hours after dosing. Urine samples were obtained at 0.5, 2, 4, 6, 8 and 24 hours after dosing. No metabolism was observed. Small chromatographic peaks seen at the solvent front were later determined to be artefacts of the analytical method.

- Excretion

Results from the studies already described suggest that unchanged gadoversetamide is rapidly eliminated in the urine in both rats and dogs (see table below).

Elimination of gadoversetamide following iv administration (% dose)

Species	Dose	Time	Urine	Faeces	Bile*	Cage	Carcass	Tot
Rat	0.1 mmol/kg	2	62.8	0.06	0.35	21.4	-	84.26
		4	73.5	0.12	0.37	23.1	-	96.72
		8	73.9	0.21	0.37	23.2	-	97.31
		24	74.1	3.22	0.37	23.2	-	100.52
		48	74.3	3.64	0.37	23.2	-	101.14
		72	75.5	3.75	-	23.2	0.0	102.45
Rat	0.1 mmol/kg	4	85.8	2.7	-	-	-	88.3
		24	84.2	5.9	-	-	-	90.1
		48	88.5	2.6	-	-	-	91.1
Rat	0.9 mmol/kg	4	85.3	0.0	-	-	-	85.3
		24	93.3	1.9	-	-	-	94.2
		48	94.8	4.3	-	-	-	99.1
Dog	0.1 mmol/kg	8	76.9	-	-	4.15	-	81.05
		24	79.6	0.60	-	3.48	-	83.68
		48	80.0	0.56	-	3.62	-	84.18
Rat nor	0.1 mmol/kg	4	78.26	0.90	-	9.47	4.93	93.56
Rat an	0.1 mmol/kg	4	0.02	0.00	-	0.00	91.83	91.84

* - different animals, nor - normal, an - anephric

- Pharmacokinetic drug interaction

No such studies were carried out as gadoversetamide is intended for single use only.

- Other pharmacokinetic studies

Due to the high renal excretion, a study was set up to examine tissue distribution and excretion in normal, anephric and sham operated male SD rats. The rats received 0.3 mmol/kg iv Gd^{153}-labelled gadoversetamide followed by sampling of blood, urine and tissues at 0.5-4 hours. Serum chemistry showed that anephria was successfully induced (increased creatinine and BUN). At 30 min post-dose most of the Gd^{153} in normal animals was in the kidneys and bladder, in anephric animals it was still in the blood, plasma and carcass. After 4 hours 91.83% of the dose remains in the tissues of the anephric animals while only 4.93% remains in normal animals. The GI-tract and liver are proposed as potential secondary elimination routes.

Toxicology

- Single dose toxicity

Single-dose toxicity testing of the gadoversetamide was conducted in mice, rats and dogs using various formulations. In addition, single-dose toxicity testing of the chelating ligand versetamide was performed using the sodium salt (mice only) or calcium complex (mice, rats and dogs).

CD-1 mice received 0, 10, 20, 25 and 30 mmol/kg gadoversetamide in Tris buffer. The minimum lethal dose was 20 mmol/kg, and LD_{50} = 25mmol/kg. In addition ICR mice, received 0, 8, 10, 12, 14 and 16 mmol/kg gadoversetamide. The minimum lethal dose was 8 mmol/kg, and LD_{50} = 10 mmol/kg. In both studies clinical signs included lethargy, tremors, pallor, staggering gait, clonic convulsion, hyperactivity, hypothermia, dyspnoea, exophtalmos and piloerection. Most deaths occurred within

days after administration, some animals died within minutes after administration. No NOAEL could be established.

In one part of the study, formulations contained constant concentrations of gadoversetamide (~0.5 M) and versetamide (~0.02 M) with varying amounts of calcium (0-0.03 M). Administration of versetamide as the sodium salt, without addition of calcium, results in a relatively toxic formulation of gadoversetamide (LD_{50} < 6 mmol/kg). The optimal formulation contained a stoichiometric ratio of calcium and versetamide. In the second part of the study, the concentration of gadoversetamide was held constant (~0.5 M), a stoichiometric ratio of calcium/versetamide was maintained, but the calcium versetamide concentration was varied (0.005-0.025 M). High LD_{50} values (~30 mmol/kg) were observed with all /calcium versetamide formulations. The LD_{50} for the calcium versetamide alone was approximately 15 mmol/kg. Hypoactivity was seen with each formulation and occasional dyspnoea and convulsions were noted. With only two exceptions, deaths were observed within the first few minutes after dosing.

There were no statistically significant differences in LD_{50}-values when different manufacturing processes or lots that were stored in either glass vials or plastic syringes were compared.

Toxicities of OptiMARK and Magnevist were compared in ICR mice. The animals received OptiMARK (16, 18, 20, 22, 24, 26, 28 mmol/kg gadoversetamide) or Magnevist (2, 4, 6 mmol/kg). Clinical signs observed in both groups consisted of dyspnoea, convulsions, hyperactivity and mild ataxia. Additionally, some of the gadoversetamide treated animals showed mild hypoactivity, tremors, prostration and unkemptness and red scaly sore areas on the tail. Surviving animals appeared normal 30 minutes after Magnevist and up to 4 hours after OptiMARK. The combined sex LD_{50} value for OptiMARK was 24 mmol/kg and for Magnevist 4.9 mmol/kg.

In rats acute intravenous toxicity of gadoversetamide was assessed (doses up to 16 mmol/kg) with special emphasis on the kidneys and testes/epididymides. There were no deaths or clinical signs of toxicity. A dose related mild vacuolation of the renal proximal convoluted tubule was observed which tended to recover by day 15. In addition in some animals' degeneration of late stage spermatids or spermatozoa in testes and epididymides was observed and could be a possible drug related effect. NOAEL with gadoversetamide is 0.5 mmol/kg.

To investigate the potential CNS neurotoxicity of OptiMARK, two single-dose toxicity studies were conducted using intracisternal injection. Rats received doses up to 0.20 mmol/kg gadoversetamide. Clinical signs included tremors, convulsions, rearing/pawing, salivation and vocalization. Most of the surviving animals appeared to be normal within 24 hours and all deaths except for one occurred within 24 hours. Intracisternal toxicity of Magnevist (0.05 and 0.1 mmol/kg) was similar in terms of clinical signs. Occasional focal lesions detected in the brain were found with a higher frequency in the Magnevist group.

In a study in Beagle dogs treated with a single intravenous dose of Tris containing gadoversetamide solution (3, 6 or 12 mmol/kg) all animals survived. There were neither treatment related physical observations nor effects on body weight, haematological results or pathological findings at necropsy after an observation period of 14 days. Slight increases in serum alkaline phosphatase and slight decreases in phosphorus levels in the 6 and 12 mmol/kg group were considered to be treatment related. NOAEL with gadoversetamide is 3 mmol/kg

- Repeat dose toxicity (with toxicokinetics)

Rats (20/sex/group) were given 0-0.1-0.6-3.0 mmol/kg/day gadoversetamide/tris i.v. for 4 weeks. There were no deaths that could be attributed to treatment. Clinical signs seen from Day 11 included erythema, ulceration encrustation and/or exfoliation of the injection site. In addition rapid irregular respiration, dry skin, poor grooming, reduced body weight accompanied by marginally lower food consumption was observed. Some top dose animals had focal corneal opacity and brown mucous discharge from the eyes, which fully recovered on withdrawal. During the recovery period generalized hair loss and scabbing or encrustation of the skin or at least ungroomed appearance was noted in males that had received 0.6 or 3.0 mmol/kg. In animals given 3.0 mmol/kg haematological

examination after 25 days of treatment showed a marked reduction in erythrocytic parameters (low haematological concentrations, erythrocyte counts) and an increase of abnormally shaped red cells, accompanied by an increase in platelet and leukocyte counts and a slightly shorter activated partial thromboplastin time in the males. Full resolution of symptoms was evident after seven weeks of respite from treatment, but not after three weeks. Macroscopic examination at necropsy after four weeks of treatment showed that testes of most males that had received 3.0 mmol/kg gadoversetamide appeared small and soft. Epididymides and prostates of most of these males were also noted to be small and to have reduced weights. Histopathological examination showed degeneration of the testicular germinal epithelium with presence of spermatid giant cells and markedly reduced sperm content in the epididymides. There was no significant recovery from these changes after four or eight weeks of recovery. Furthermore, there is evidence from the reproductive toxicity studies that there is an irreversible loss of germinal epithelium in the majority of semiferous tubules after a recovery period of 8 or 19 weeks. The absolute and relative kidney weight of males and females treated with 3.0 mmol/kg gadoversetamide was significantly elevated at the end of treatment and after the four week recovery period and still slightly higher after eight weeks. Histopathological examination revealed macro and micro-vacuolization of the cytoplasm in proximal convoluted tubules in some male rats of the mid-dose group and all animals of the high-dose group. After four weeks of treatment examination of the stomach of several males that had received 3.0 mmol/kg revealed thickening of the glandular mucosa and some punctate dark areas, which were identified as red blood cells. These findings were reversible after the recovery period. NOAEL of gadoversetamide is 0.1 mmol/kg.

A comparative repeated dose toxicity study was performed in rats of gadoversetamide with three concentrations of the stabilizer calcium versetamide. Three groups of 4 male rats received intravenously doses of 5 mmol/kg gadoversetamide containing either 1 %, 5 % or 10 % versetamide for 5 days. Fur loss and skin lesion were observed in all animals treated with gadoversetamide. The onset of skin lesions occurred earlier in the 10% calcium versetamide group. This group also had lower tissue (liver, spleen skin) concentrations of gadolinium.

Beagle dogs received gadoversetamide 0-0.1-0.5-1.0 mmol/kg/day i.v. for 28 days. Two animals of the high-dose group died. Prior to death, both animals showed lethargy, uncoordinated movements, tremors, decreased food consumption and watery and discoloured stool. The other males of the high-dose group had decreased food consumption and decreased body weight gain during the treatment period. The female animal, which was sacrificed in moribund condition, showed signs indicative of renal malfunction and electrolyte imbalance, consisting of a significant decrease in calcium and an increase in phosphorus levels. There were no signs of adverse effects in ophthalmic or haematological evaluations. A dose related reduction in serum phosphorus and increase in serum chloride during treatment as well as a marked decrease in urinary calcium levels at the end of the treatment period were observed. All values of the surviving animals returned to normal at the end of the recovery period (8 weeks). At necropsy there was dose related, reversible tan discoloration of kidneys and bilateral vacuolation of the epithelium of the convoluted tubules in the kidney. The kidney weights were significantly increased in these animals. At the end of the 8-week recovery period some recovery was evident, but the values of the high-dose group remained still slightly higher compared to controls. At the end of the recovery period the kidneys were microscopically normal.

In order to evaluate the effect of repeated doses of gadoversetamide on urine calcium levels, 2 additional dogs were given 3 mmol/kg for 12 days. Dogs were sacrificed because of their moribund condition. Urine calcium levels of daily collected urine samples were investigated by spectrophotometry and atomic absorption. Both methods showed no meaningful treatment related decrease in urine calcium as observed in the main study. The presence of OptiMARK in the urine had been shown not to interfere with these analytical methods. The NOEL for gadoversetamide is 0.1 mmol/kg.

- Genotoxicity

The mutagenic potential of OptiMARK has been assessed in a battery of standard in vitro and in vivo tests. With the exception of the in vitro chromosomal aberration assay all tests showed negative results. The clastogenic effects were associated with severe cytotoxicity (decreased of mitotic index

and decreased cell number). In an in vivo assay evaluating the potential induction of micronucleated polychromatic erythrocytes in the bone marrow of mice OptiMARK was found to be non-clastogenic. Structural and numerical chromosome aberrations observed in vitro at very high concentrations were not considered as relevant for the in vivo situation. Thus, under conditions of recommended clinical use is regarded as safe with respect to genotoxicity.

- Carcinogenicity

No studies are required as the product is for single dose only.

- Reproduction Toxicity

Fertility and early embryonic development

Rats were given 0, 0.1 and 0.5 mmol/kg/day OptiMARK. The males from week 9 pre-mating to day 21 post-partum, the females from week 2 pre-mating to day 20 of gestation or day 21 post-partum. Male animals at 0.5 mmol/kg showed reduced weight gain from the start of the mating period (study week 10). No obvious toxicity was apparent in females. Mating performance and fertility were unimpaired. Two of the top dose females had total litter abortion/resorption. There were no adverse effects on in utero litter development (corpora lutea, implantation, losses, number, sex ratio, etc). Parturition, postnatal development, maturation and fertility of the F1 generation appeared to be unaffected, except for a slight reduction in F1 pup growth rate from birth to Day 8 postpartum and a lower absolute body weights at age 28 days of the F1 generation at 0.5 mmol/kg.
The NOEL in this study was 0.1 mmol/kg.

As part of the above study a group of males received 2 mmol/kg/day. Treatment was terminated after 7 weeks due to excessive toxicity (reduced body weight gain and food consumption, skin effects, periorbital discharge, pale extremities, 2 deaths). Animals were subsequently sacrificed or mated with untreated females after a 4-8 week recovery period. Mating was normal after 4 weeks recovery but only 1/12 females became pregnant; after 8 weeks recovery 2/12 mated 1/12 became pregnant. Spermatogenesis was severely inhibited with depletion of stem cells and there was little or no recovery after treatment had been withdrawn for a total of 19 weeks. Similar changes were observed in a 28-day repeated dose study in rats where testis, epididymis and prostate weights were reduced in the high dose given 3 mmol/kg/day. Histopathology showed degeneration of the atrophic testicular tubules, spermatid multinucleated cells and absence of mature spermatozoa and presence of round spermatids in epididymides.

Embryo-fœtal development

Pregnant rats SD were given 0-0.1-0.7-4.9 mmol/kg/day gadoversetamide on days 7-17 of gestation. Prenatal effects were restricted to the high dose (4.9 mmol/kg/day) with decreased maternal food consumption and body weight gain during the treatment period. Some skeletal and visceral variants (unossified sternebrae, abnormal liver lobation) occurred with a higher frequency. Postnatal development of offsprings remained largely unaffected. The top dose was associated with subtle developmental delays (startle response and air righting reflex). NOEL = 0.7 mmol/kg.

Pregnant rabbits received 0, 1, 2 or 4 mmol/kg from Day 6 through Day 18 of pregnancy in a preliminary dose-ranging study of gadoversetamide. Treatment with 4 mmol/kg/day produced severe weight loss and reduced food intake. At necropsy, pale/enlarged kidneys were seen in 5/6 high-dose animals. At 1 and 2 mmol/kg/day, similar less-pronounced effects on body weight and food consumption were seen in the pregnant females and there were a slightly higher number of malformed foetuses compared to saline controls. In the pivotal study pregnant rabbits were given 0-0.1-0.4-1.6 mmol/kg gadoversetamide from day 6-18 of gestation, with caesarean section on day 29. The dams showed no clinical signs of toxicity apart from a slight loss in body weight gain at the top dose. There was a slight, dose related increase in the number of litters and the number of foetuses showing forelimb flexure or hind limb malrotation and cardiovascular defects. Maternal NOEL = 0.4 mmol/kg. Foetal NOEL = 0.1 mmol/kg.

Prenatal and postnatal development, including maternal function

A dose ranging study (0.5, 1.5 or 4.5 mmol/kg/day) was carried out in rats, there was no dose limiting toxicity. Pregnant rats were given 0-0.1-0.7-4.2 mmol/kg/day gadoversetamide from day 17 of

gestation to Day 22 post-partum. The only effect in female rats treated during late pregnancy and during lactation was a red-brown periorbital staining during the last week of lactation in the high dose group. There was no effect on gestation index but high implantation losses were recorded for two top dose dams. Fertility of the F1 animals was normal.

- Local tolerance

OptiMARK was compatible with (human) RBC's and plasma proteins in vitro. Administration of gadoversetamide in arteries in rabbits induced minimal to moderate venous inflammation caused by the trauma of the injection. Subcutaneous and intra-muscular injection of gadoversetamide produced a similar degree of irritation as induced by saline but did appear to be more persistent.

- Other toxicity studies

Antigenicity

The antigenicity of gadoversetamide was investigated in guinea pigs and mice/rats. Guinea pigs were sensitized by subcutaneous injections of gadoversetamide. Sera from these animals were subsequently used for homologous passive cutaneous anaphylaxis reaction (PCA), passive hemagglutionation reaction (PHA) and active systemic anaphylaxis reaction (ASA). Gadoversetamide or gadoversetamide coupled to guinea pig serum albumin (GVS-GSA) were used as challenging agents. A weak antigenicity of gadoversetamide was observed only in the ASA test when GVS-GSA was used as a challenging agent. Heterologous PCA testing was conducted in rats using sera from two different strains of sensitized mice. Challenges were done with gadoversetamide or gadoversetamide coupled to rat serum albumin. No positive results were obtained.

Immunotoxicity

No other immunotoxicity studies were conducted with OptiMARK. There were no signs of compromised immune function or sensitization in animals receiving daily repeat-doses for periods ranging from 4 to 18 weeks.

Studies on impurities

Impurities present in OptiMARK are closely related to the active substance, gadoversetamide, and to the stabilizer, versetamide, and fall into the category of polyamino polycarboxylates and their derivatives.

Single dose studies with a 14-day observation period were conducted in the mouse. Impurities were administered at doses that were either at the maximum quantity that would be present in OptiMARK, based on specification limits, or that were significant multiples of the doses that would be achieved clinically. All five specified impurities had very good safety margins relative to their specifications. No toxic effects were seen with any of the four polyaminocarboxylate compounds (NOAEL doses for each were the highest doses administered).

One newly identified impurity was identified in new production lots. It arises from trace amounts of ammonia present in MEA used in the production of versetamide. The amount of ammonia increased slightly after production changes by the supplier. It has proven difficult to synthesize this impurity for toxicity testing. Up to 0.3%, it is considered that this impurity will not alter the safety profile of OptiMARK.

Impurities, if present, would be at extremely low levels and the majority would be present as calcium or gadolinium chelates. Based on their structural similarities to the contrast agents and other compounds with known toxicity the analysis of potential impurity toxicity concluded that these potential impurities would present no risk in OptiMARK

Other studies
Three *in vitro* tests were employed to study the cytotoxicity, mutagenicity and haemolytic effects of molded syringe barrels. Extracts of the syringe barrels in cell culture medium were non-cytotoxic in the ISO Elution assay to mouse L-929 fibroblasts. Saline extracts of syringe barrels were non-mutagenic in the Ames test. Saline extracts of syringe barrels were non-haemolytic when incubated with diluted rabbit blood.

The USP systemic toxicity test for class VI plastic used extracts of syringe barrels was done in mice. Extracts of syringe barrels were prepared in saline, ethanol/saline (1:20), polyethylene glycol (PEG) and cottonseed oil and another extracts were prepared in Optiray 350 (*containing an iodine X-ray contrasting agent*) or OptiMARK. There was no mortality or evidence of systemic toxicity of the extracts during a 72-hour observation period after dosing, except for extracts prepared in Optiray 350. The animals receiving Optiray 350 appeared lethargic immediately after dosing. However a ten mouse retest was conducted in which no mortality or evidence of systemic toxicity was observed.

The saline extract of syringe barrels was intradermally injected and occlusively patched in a guinea pig sensitization test. The saline extract showed no evidence of delayed dermal contact sensitization when patches were challenged after a 14-day recovery period.

The saline extract of syringe barrels was intravenously injected via the marginal ear vein of New Zealand White rabbits. The maximum change in rabbit temperatures during the 3 hours observation period was $\leq 0.2^{o}C$ which is within acceptable limits. The test solution was judged as nonpyrogenic. Additionally extracts of syringe barrels were prepared in saline, ethanol/saline, PEG and cottonseed oil and injected intracutaneously in New Zealand White rabbits. There was no evidence of irritation or toxicity from the extracts. Also in rabbits, sterile samples of syringe barrels were aseptically implanted in muscle for an intramuscular toxicity test. The implanted syringe material did not elicit a macroscopic reaction and was considered as non-irritant.

Ecotoxicity/environmental risk assessment

The values for $PEC_{SURFACEWATER}$ for both gadoversetamide and versetamide have been incorrectly calculated. After the correction both values are greater than the phase I limit of 0.01 microg/l. A Phase II assessment has not been conducted.

Discussion on the non-clinical aspects

Pharmacology

The primary pharmacodynamic effect of OptiMARK, a gadolinium chelate based MRI contrast agent, has been demonstrated by its effect on tissue proton relaxation times (T1 and T2) and impact on the clarity of the MRI image. Gadolinium chelates have already shown their therapeutic efficiency in the field of MRI. Pharmacodynamic studies presented here have shown that the imaging effects of OptiMARK and Magnevist (a standard gadolinium chelate available in the market) are quantitatively equivalent. The equivalence on qualitative grounds may be however questionable. Direct comparison of efficacy of OptiMARK against Magnevist was made only in clinical studies, where OptiMARK was shown to be non-inferior to Magnevist.

The safety pharmacology studies clearly set out that effects on the QT interval are unlikely to occur. The effects of OptiMARK and other agents were mimicked by comparable increases in osmolarity produced by mannitol. These results suggest that OptiMARK caused prolongation of cardiac action potentials largely as a result of hypertonicity rather than specific ion-channel interactions. These *in vitro* effects were observed only at the highest concentration, which was at least 100x the maximum plasma concentration that would be achieved under conditions of clinical use. No significant effect on QT interval was noted either in the *in vivo* safety pharmacology studies that used of 10x doses in excess in the proposed clinical use.

Pharmacokinetics

Gadoversetamide, the active active substance in OptiMARK, appears to have an appropriate pharmacokinetic profile for its intended application as an extracellular magnetic resonance contrast agent. Gadoversetamide distributes between plasma and interstitial fluid, does not penetrate the blood-brain barrier, undergoes minimal passage of the placental barrier and is rapidly excreted in urine in unchanged form. It is known that the clearance of gadolinium-derivatives is highly delayed in patients with renal insufficiency, therefore excretion might be a problem in this type of patients.

A low residual level of radioactivity (~ 0.2-0.3 % of the injected dose) in the rat skeleton was found to be constant over a 4-7 day interval after administration of Gd^{153} OptiMARK. Data for these studies were consistent with published reports showing residual radioactivity in the bones of rodents, days after administration of a single dose of Gd^{153} labelled commercial products. The absence of toxicological effects on bone makes this issue a minor concern.

No pharmacokinetic studies were carried out after repeated administration. Although the product is intended for single use only, data on repeated administration might be useful to support repeated dose toxicity studies.

Toxicity

Studies with OptiMARK did not elicit classical signs of single-dose gadolinium toxicity. Specifically with respect to cardiotoxicity, extensive pharmacology safety testing demonstrated a very high degree of cardiovascular safety for OptiMARK and it compared very favourably with other commercially available agents.

There appears to be an effect on male reproduction that is permanent. There were still marked numbers of atrophic testicular tubules accompanied by minimal diffuse interstitial cell hyperplasia 8 and 19 weeks after dosing was stopped. No mature spermatozoa were seen in rats after 19 weeks recovery, only some slight reversibility in the small number of tubules where germinal epithelium survived. The effects on male reproduction have not been considered of clinical concern because the effects were not noted in single dose toxicity studies, and the intended clinical application is for one use only.

There is also a potential for serious adverse effects in foetal development. Increases in skeletal and visceral variations, some delays in the attainment of reflexes and increased prevalence of postural limb anomalies and of cardiovascular malformations have been described in rats and rabbits following repeated exposure to gadoversetamide. The threshold of adverse effects for the foetus appears to be below a clearly toxic level for the mother. The proposed indication involves a single administration and serious reproductive effects would not be anticipated, nonetheless, caution in the use of gadoversetamide in pregnant women is warranted and has been highlighted accordingly in the SPC.

4. Clinical aspects

GCP

According to the applicant, the clinical trials used to support this marketing authorization application were designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) regulations. All studies were conducted in accordance with the Declaration of Helsinki and recent revisions.

Pharmacokinetics

Clinical pharmacology studies included two *in vitro* plasma protein-binding studies and two in vitro human blood compatibility studies were conducted and clinical studies performed to evaluate the safety, pharmacokinetics and pharmacodynamics of OptiMARK.

In addition, seven studies (5 phase I, 1 phase II, and 1 phase IV) were conducted in which the pharmacokinetics of OptiMARK was examined in normal healthy volunteers (adult and paediatric subjects) and patients with various central nervous system (CNS) and liver pathologies as well as various renal and hepatic functions. These studies are summarised in the following table:

Tabular Listing of OptiMARK Clinical Pharmacology Studies

Type of Study	Study Start/ End dates	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients
PK Phase 1 433	Mar 1993 Apr 1993	First-in-human study Safety, tolerance and pharmacokinetics	Double-blind, ascending dose, randomized, placebo-controlled, parallel-group, single-centre study	OptiMARK Single ascending doses: 0.1, 0.3, 0.5 and 0.7 mmol/kg Placebo (normal saline) IV injection	20 4 groups of 5 volunteers (4: test product; 1: placebo)	Healthy male volunteers aged 18 to 45 years
PD, PK Phase 1 489	Jun 1996 Aug1997	Pharmacodynamic dose-related effects, pharmacokinetics, safety and tolerability	Double-blind, randomized, placebo-controlled, parallel-group, single-dose, multicentre study	OptiMARK Single doses: 0.1, 0.3 and 0.5 mmol/kg Placebo (normal saline) IV injection	201 enrolled 171 randomized 163 evaluable	At least 2 years of age, liver or CNS pathology with or without renal insufficiency
PK Phase 1 538	Jun 1997 Nov1997	Pharmacokinetics, safety and tolerance	Open-label, single-dose, multicentre study	OptiMARK 0.1 mmol/kg IV injection	58 enrolled 54 dosed	At least 18 years of age, healthy or with CNS or liver pathology, with or without renal insufficiency
PK Phase 1 543	Oct 1997 Nov 1997	Pharmacokinetics, dialysis clearance rate and safety	Open-label, single-dose, single centre study	OptiMARK 0.1 mmol/kg IV injection	10 enrolled 8 dosed	At least 18 years of age, end-stage renal disease maintained on haemodialysis

Type of Study	Study Start/ End dates	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients
PK Phase 1 552	Jun 1998 Jul 1998	Pharmacokinetics, safety	Open-label, single-dose, single centre study	OptiMARK 0.1 mmol/kg IV injection	27 enrolled 17 dosed	Healthy paediatric subjects aged 2 to 18 years
PK/PD Phase 2 789	Sep 2003 Aug 2004	Pharmacodynamics, safety and pharmacokinetics	Open-label, cross-over, single-dose, single centre study	OptiMARK, Magnevist, Omniscan, and ProHance 0.1 mmol/kg IV injection	28 enrolled 26 dosed	Healthy male and female volunteers aged 18 or older
Safety Efficacy PK Phase 4 597	May 2002 Dec 2003	Safety, efficacy and pharmacokinetics	Open-label, single-dose, multicentre study	OptiMARK 0.1 mmol/kg IV injection	105 enrolled 100 evaluable for safety 98 evaluable for efficacy 30 evaluable for pharmacokinetics	Paediatric patients, aged from 2 to 18 years, with suspected CNS or liver pathology

IV: intravenous; CNS: central nervous system

METHODS

In vitro
The in-vitro studies confirmed the absence of any binding of the product to plasma proteins and confirmed the blood compatibility of OptiMARK.

In vivo
Validated analytical methods were used to measure gadoversetamide [liquid chromatography (HPLC-UV) or liquid chromatography-tandem mass spectrometry (LC/MS/MS)] and/or gadolinium [inductively-coupled plasma-mass spectrometry (ICP-MS) or inductively-coupled plasma-atomic emission spectrometry (ICP-AES)] in serum (or plasma) and urine of clinical studies.

- Absorption

No biopharmaceutic (bioavailability, bioequivalence, food effect, etc.) studies of gadoversetamide were performed.

- Distribution

At the 0.1 mmol/kg dose, the mean $t_{1/2\alpha}$ in normal subjects calculated by the method of residuals in 12 normal volunteers (studies 489 and 538) is 13.3 ± 6.8 min.
Mean V_{DSS} at the 0.1 mmol/kg dose in non-renally impaired patients (including both normal subjects and patients with CNS or liver pathology) range from 158.7 ± 29.0 to 214.3 (range 116.4 to 295.0) mL/kg (studies 538 and 789, respectively). This volume of distribution (approximately 10-15 L for a body weight of 70 kg) is consistent with a drug that distributes into the extracellular fluid.
Gadoversetamide does not undergo protein binding in vitro.
In pregnant and lactating rats that received radiolabelled gadoversetamide, radioactivity was detected in the placenta, foetus and maternal milk.

- Elimination

The $t_{1/2}$ at the 0.1 mmol/kg dose range from 1.49 ± 0.15 hr in healthy volunteers (study 433) to 2.11 ± 0.62 hr in non-renally impaired patients (including normal subjects and patients with CNS or liver pathology) (study 538).

The mean plasma clearance of OptiMARK in healthy subjects (111.0 ± 14.1 mL/min/1.73m^2 BSA) is not significantly different from the mean renal clearance (study 433). Similar results are obtained in all subjects of study 538 (including normal subjects and patients with various combinations of liver, CNS and renal dysfunctions) with renal clearance of OptiMARK being approximately 95% of the total plasma clearance.

OptiMARK is eliminated into the urine as the intact complex, as it is not metabolized in humans, with a mean of 95.5% eliminated within 24 hours

- Dose proportionality and time dependencies

The pharmacokinetics of OptiMARK appear to be linear within the dose range (0.1 – 0.7 mmol/kg) studied. Dose level has no consistent effect on V_{DSS} in any of the studies. The $AUC_{0-\infty}$ is dose proportional, regardless of the renal status, within an OptiMARK dose range of 0.1-0.5 mmol/kg (study 489).

Statistical analysis of the pharmacokinetic parameters showed no significant differences ($p<0.05$) between the 4 gadolinium chelates OptiMARK, Magnevist, Omniscan and ProHance for the elimination $t_{1/2}$, V_{DSS}, $AUC_{(0-t)}$ and CL_T.

- Special populations

At each dose level examined, $AUC_{0-\infty}$ was increased 3- to 4-fold in the renally-impaired group versus the non renally-impaired group. The effect of renal impairment on V_{DSS} appeared to increase the volume slightly, by about 20-70 mL/kg. Total plasma clearance decreased by about 50 mL/hr/kg in the renally-impaired groups. The $t_{1/2}$ ranged from means of 7.8 to 8.9 hours in the renally-impaired groups. These 3- to 4-fold changes in clearance and half-life are consistent with the differences in $AUC_{\mathbf{0}-\infty}$. Renal impairment has been shown to delay the elimination of gadoversetamide (mean elimination half-life of 7.83 ± 3.8 hours). The mean cumulative urinary excretion of gadoversetamide at 72 hours was approximately 93.5 % for renal impaired patients and 95.8% for subjects with normal renal function. The mean dialysis clearance of gadoversetamide, estimated from the recovery rate in dialysate was 93.2 ± 17.1 mL/min or 48% of the creatinine clearance (194 ± 18.6 mL/min).

The $AUC_{\mathbf{0}-\infty}$, a surrogate endpoint of systemic exposure, shows that exposure to OptiMARK increases significantly with age. When corrected for body weight, the total body clearance of OptiMARK is greater in the 19 to 64 year age group (82.1 ± 16.8 mL/hr/kg) than that observed in the ≥ 65 year of age group (56.5 ± 9.7 mL/hr/kg). The $t_{1/2}$ in the 19 to 64 is shorter than that observed in the ≥ 65 year of age group (1.9 ± 0.5 and 2.5± 0.5 hr^{-1}, respectively).

No effects of hepatic impairment neither of gender on pharmacokinetic parameters and urinary recovery were observed.

The $AUC_{\mathbf{0}-\infty}$ of the youngest subjects (2 to 11 year age group) is smaller than that observed in adults ≥ 65 year of age (114 ± 25.7 versus 285 ± 54.1 µg x hr/mL). When corrected for body weight, the total body clearance of OptiMARK is greater in the 2 to 11 year age group (143 ± 27.9 mL/hr/kg) than that observed in the 12 to 18 year age group (117 ± 26.1 mL/hr/kg). When corrected for body surface area, the total body clearance of OptiMARK is similar for the 2 to 11 and 12 to 18 year age groups (3847 ± 879 and 4239 ± 719 mL/hr/m^2, respectively) but is greater than that observed in the two adult populations (3363 ± 664 and 2209 ± 268 mL/hr/m^2 in the 19 to 64 and ≥ 65 year of age groups, respectively). The V_{DSS} in the 2 to 11 and 12 to 18 year age groups (216 ± 39.1 and 212 ± 36.2 mL/kg, respectively) is higher than that observed in the two adult populations (175 ± 33.7 and 161 ± 8.4 mL/kg, respectively). The $t_{1/2}$ in the 2 to 11 and 12 to 18 year age groups (1.4 ± 0.3 and 1.6± 0.3 hr^{-1}, respectively) is shorter than that observed in the two adult populations (1.9 ± 0.5 and 2.5± 0.5 hr^{-1} in the 19 to 64 and ≥ 65 year of age groups, respectively).

- Pharmacokinetic interaction studies

No studies performed

Pharmacodynamics

- Mechanism of action

The purpose of a gadolinium–containing MRI contrast agent is to induce signal intensity changes within a lesion, thereby facilitating its recognition from the surrounding normal structures. This is done by the use of the metal gadolinium which, due to its atomic structure, acts indirectly on the local magnetic environment to alter proton T1 relaxation times. The clinical utility of MRI contrast agents depends on both the relaxivity of the agent and the relative concentrations present in tissues of interest at the time of imaging. Differing rates of contrast agent diffusion into and out of lesions and normal surrounding tissues significantly increases the ability to detect and characterize lesions.

- Primary pharmacology

Study 789 compared the contrast-to-noise time-intensity curves for OptiMARK among three extracellular gadolinium chelates currently on the European market: Omniscan, Magnevist and ProHance.

The four gadolinium chelates produced an increase in the contrast-to- noise ratio for the Regions of Interest (ROIs) measured in the abdominal aorta, liver parenchyma, portal vein, renal cortex and renal medulla. No statistically significant differences were detected among the four gadolinium chelates for the contrast-to-noise time-intensity curves parameters: I_{max}, T_{max}, AUC_{tmax} and AUC_t, for the 5 ROIs except for some differences in the renal medulla ROIs. The 90% confidence intervals of the ratios of I_{max}, AUC_{tmax} and AUC_t, comparing OptiMARK to Magnevist, all fell within the standard pharmacokinetic bioequivalence interval of 80% and 125%. These confidence intervals were also within the proposed estimated Imaging Equivalence Interval with a few exceptions, which occurred in renal medullary ROIs.

- Secondary pharmacology

OptiMARK produces transient decreases in serum zinc and transient increases in urinary zinc (Study 489 shows an increased excretion of 8mg zinc at the 0.1 mmol/kg dose in the first 24 hrs post-dose). OptiMARK has no apparent effect on serum or urine iron levels (Study 489 demonstrated an increase in excretion of < 0.3 mg more iron than placebo at the 0.5 mmol/kg dose)

After the administration of OptiMARK and Omniscan, serum calcium levels did not change significantly when measured by the ICP-MS and AZ-III techniques. However, the OCP method reported transient decreases in calcium values immediately after injection of these two agents. None of the analytical methods used detected any significant change in serum calcium after the injection of Magnevist and ProHance.

Clinical efficacy

Two pivotal phase 3 CNS studies (Study 488 and Study 525) and the two pivotal phase 3 liver studies (Study 490 and Study 526) were considered as supportive to the claimed indications and the results of the re-read are fully presented in the marketing authorisation application.

Because the two pivotal phase 3 CNS studies and the two pivotal phase 3 liver studies were similar in terms of indication, study objectives, study design, efficacy endpoints and statistical analyses, the data is presented together.

Key Features of the Clinical Studies Supporting the Claims for Efficacy of OptiMARK (Re-read Phase 3 Pivotal Studies)

Study #	Study Start/ End dates	Re-read Start / End dates	Objective(s) of the Re-read	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Study Population	Number of Patients
525	Jun 19, 1996 Mar 17, 1997	Jul 13, 2005 Dec 30, 2005	To demonstrate non inferiority of OptiMARK versus Magnevist as assessed by the change in contrast score from pre to post-contrast images	Phase 3, double-blind, randomized, active-controlled, parallel-group, single-dose, multicentre study	OptiMARK 0.1mmol/kg Magnevist 0.1mmol/kg IV injection	At least 18 years of age, with known or highly suspected CNS pathology (brain or spine)	195 enrolled 195 randomized: 129 OptiMARK; 66 Magnevist 194 re-read: 129 OptiMARK; 65 Magnevist
488	Jan 15, 1996 May 31, 1997	Jun 25, 2005 Dec 30, 2005	To demonstrate non inferiority of OptiMARK versus Magnevist as assessed by the change in contrast score from pre to post-contrast images	Phase 3, double-blind, randomized, active-controlled, parallel-group, single-dose, multicentre study	OptiMARK 0.1mmol/kg Magnevist 0.1mmol/kg IV injection	At least 18 years of age, with known or highly suspected CNS pathology (brain or spine)	208 enrolled 206 randomized: 136 OptiMARK; 70 Magnevist 201 re-read: 133 OptiMARK; 68 Magnevist
526	Aug 20, 1996 Jun 3, 1997	Jul 28, 2005 Jan 3, 2006	To demonstrate non inferiority of OptiMARK versus Magnevist as assessed by the change in contrast score from pre to post-contrast images	Phase 3, double-blind, randomized, active-controlled, parallel-group, single-dose, multicentre study	OptiMARK 0.1mmol/kg Magnevist 0.1mmol/kg IV injection	At least 18 years of age, with known or highly suspected liver pathology	212 enrolled 206 randomized: 102 OptiMARK; 104 Magnevist 202 re-read: 100 OptiMARK; 102 Magnevist
490	Feb 5, 1996 Apr 29, 1997	Aug 3, 2005 Jan 6, 2006	To demonstrate non inferiority of OptiMARK versus Magnevist as assessed by the change in contrast score from pre to post-contrast images	Phase 3, double-blind, randomized, active-controlled, parallel-group, single-dose, multicentre study	OptiMARK 0.1mmol/kg Magnevist 0.1mmol/kg IV injection	At least 18 years of age, with known or highly suspected liver pathology	198 enrolled 197 randomized: 100 OptiMARK; 97 Magnevist 193 re-read: 99 OptiMARK; 94 Magnevist

- Dose response studies

Four studies: **464**, **465**, **467** (phase 2) and **489** (phase 1) were conducted in patients with CNS/liver diseases utilizing more than one dose. The 3 phase 2 trials were similar in design and were conducted in 258 dosed patients to evaluate the dose-related safety, tolerance and efficacy of OptiMARK for use in MRI of the Brain (Study 464), Spine (Study 465), and Liver (Study 467). These trials utilized a cross-over, randomized, double-blind design evaluating two of the following OptiMARK doses 0.1, 0.2, 0.3, 0.4, or 0.5 mmol/kg. The results from these studies demonstrated safety and efficacy of OptiMARK at the dose of 0.1 mmol/kg and were used to design the pivotal phase 3 Brain/Spine and Liver clinical studies.

All non-clinical data indicated that the in vitro and in vivo behaviour of OptiMARK was the same as Magnevist for which the recommended standard dose is 0.1 mmol/kg.

Several studies published in the literature also support a dose of 0.1 mmol/kg of gadolinium as being an efficacious dose. Gadodiamide (Omniscan), another gadolinium chelate was approved by FDA at a dosage of 0.1 mmol/kg. This dosage was also prescribed on the basis of non-clinical imaging studies showing safety of this dose and comparable published studies of Gd-DTPA (Magnevist), taking into account that the relaxivity of the two compounds was the same.

- Main studies

Four pivotal studies were conducted in patients with known or highly suspected CNS pathology (**Studies 525 and 488**) and liver pathology (**Studies 526 and 490**). These were presented in the original MAA in 1998 that was subsequently withdrawn. After consultation with CHMP through a scientific advice application in 2005, the Company proposed the creation of a new, independent database, to be accomplished by subjecting the original images of the phase 3 pivotal studies to a new and complete blinded re-read. Accordingly these studies were re-submitted.

METHODS

Study Participants

The pivotal studies were multicentre, double-blind, randomized, parallel group, single-dose studies comparing the safety, efficacy, and tolerability of OptiMARK and Magnevist. Adult male and female subjects who were at least 18 years of age with known or highly suspected CNS (Studies 525 and 488) or liver pathology (Studies 526 and 490) were eligible.

A total of 813 subjects were enrolled, 804 were randomised, 467 received OptiMARK and 337 received Magnevist at the 0.1 mmol/kg dose level. There were no clinically meaningful differences in the demographics between the treatment groups.

Treatments

Subjects for these studies received either 0.1mmol/kg of OptiMARK or Magnevist, hand-administered by intravenous bolus injection.

All patients were scanned on a commercially available MRI device. In patients with CNS pathology, the following sequences were acquired prior to contrast agent administration:

- patients scheduled for an intracranial MRI examination received T1-weighted (short TR, short TE), T2-weighted (long TR, long TE) and Proton Density (long TR, short TE) images using imaging parameters and an imaging plane determined by the principal investigator.
- patients scheduled for a spinal MRI examination received T1-weighted Spin Echo and T2-weighted Spin Echo images using imaging parameters and an imaging plane determined by the principal investigator.

Post-contrast images after OptiMARK or Magnevist administration were a repeat of the pre-contrast T1-weighted sequence using the same imaging plane and same acquisition parameters in order to obtain identical sets of pre and post-contrast images for direct comparison.

In patients with liver pathology the following sequences were acquired prior to contrast agent administration: T1-weighted Spoiled Gradient Echo images and T2-weighted Fast/Turbo Spin Echo or

conventional Spin Echo images covering the entire liver in the axial plane using sequence parameters determined by the principal investigator.
Post-contrast images after contrast agent administration were T1-weighted Spoiled Gradient Echo using the same imaging plane and same acquisition parameters as pre-contrast series in order to obtain identical sets of pre and post-contrast images for direct comparison. Post-contrast images were acquired at the following times in order to capture the arterial, venous portal and equilibrium (delayed) phases:

- 15-25 seconds after the initiation of the bolus injection (arterial phase),
- 55-65 seconds after the initiation of the bolus injection (portal phase),
- and, ~5 minutes after the initiation of the bolus injection (delayed phase).

In the liver studies all patients were scanned using a 1.5 Tesla MR unit.
In the CNS studies the majority of patients (312/389, 80.2%) were scanned using a 1.5 Tesla MRI unit. The remainder were scanned using field strengths less than 1.5 Tesla (range 0.3 to 1.0 Tesla). The proportion of patients imaged at field strengths less than 1.5 Tesla were the same for both contrast agents.

Objectives

Primary objective was to demonstrate the non-inferiority of OptiMARK versus Magnevist as assessed by the change in contrast score between pre and post-contrast images. The primary efficacy endpoint was a contrast score taking into account lesion delineation, lesion conspicuity and contrast enhancement. Contrast score is assessed using a 4-point rating scale where grade 0 = no contrast, grade 1 = equivocal, grade 2 = good, and grade 3 = excellent.

Secondary objectives were to compare OptiMARK and Magnevist with respect to the following secondary efficacy radiological endpoints:

- Change in contrast scores as assessed from pre to pre+post-contrast images
- Sensitivity, specificity and accuracy
- Assessability to characterize a lesion
- Quantitative assessment of contrast enhancement on pre and post-contrast images
- Relative variation of signal intensity measurement at lesion level
- Qualitative assessment of contrast enhancement
- Change in the total number of detected lesions as assessed on pre and pre+post-contrast images
- Adequacy of images for a first diagnosis based on T1 weighted sequences
- Change in first diagnosis confidence score as assessed from pre to post-contrast images.
- Adequacy of images for an overall diagnosis based on all imaging sequences

For each treatment group and for all treatment groups combined, a comparison between pre and post-contrast images was also performed for the contrast score.
Inter- and intra-reader variability for the contrast score and the overall diagnosis and intra-reader variability for signal intensity measurements were also assessed.

Outcomes/endpoints

Radiological Assessments
The radiological variables were assessed at three different levels: imaging sequence, lesion and patient level. From these primarily assessed variables, derived variables such as contrast difference scores, sensitivity, specificity, etc. were computed.
Assessments at imaging sequence level
For each reading (pre, pre+post, post) and for each imaging sequence, evaluation of technical quality of images was performed by the blinded readers with respect to (1) Image quality: (1 = poor; 2 = fair;3 = good), (2) Assessability of images: (yes/no question), (3) presence of significant artifacts: Yes/No question.

Assessments at lesion level

For each reading (pre, pre+post, post), the blinded reader was asked to score and record a maximum of 3 clinically significant lesions on T1 sequences only. For each lesion, the following attributes were assessed: (1) T1 sequence phase on which the contrast score is the highest (for liver studies only), (2) contrast score, (3) lesion characterization, (4) signal intensity measurements, (5) qualitative assessment of contrast enhancement, (6) first diagnosis confidence, (7) lesion location, (8) lesion aspect, (9) lesion size (for liver studies only)

Assessments at patient level

For each reading (pre, pre+post, post) and considering all imaging sequences together [T1, T2 and PD (for CNS only)], the following attributes were assessed: (1) overall diagnosis, (2) overall diagnosis confidence, (3) final characterization of the patient, (4) final diagnosis: harmonized by the expert of concordance based on the final diagnosis documented in the investigator's CRF and (5) total number of detected lesions in CNS or liver studies recorded by the blinded reader.

Sample size

Power simulations were carried out to verify that a correct inference could be drawn from the new reading protocol and the new objective of non-inferiority. These Monte Carlo simulations also tested the proposed ANOVA model performances on the change in contrast score, given the actual sample size, (using several distributions for the change in contrast score).

Monte Carlo simulations were performed on study 525 and on data pooled from CNS studies (525 and 488) as these studies exhibited the greatest disparity in patient numbers between the two contrast agents and therefore would be the least powered studies.

Simulations results showed that for a possible expected difference of -0.35 and with Δ = -0.50, the non-inferiority test power remains acceptable (> 80%). For the smallest study (study 525), power points below 80% correspond to distribution types that are not expected (Exponential increasing and Bimodal). For greater sizes, the power remained constantly above 80%. The ANOVA model appeared to have a satisfactory robustness for expected distribution types.

Blinding (masking)

An independent CRO conducted the re-reading of all the MR images according to a blinded centralized reading protocol. Three independent and blinded readers re-read each of the 4 studies (12 readers in all), allowing for assessment of reader variability. After completion of the blinded reading, a fourth independent expert for each study (called expert of concordance) performed a concordance assessment. Blinded readers and experts of concordance were selected based on their professional expertise (board-certified radiologists) and training in CNS or liver MR imaging. To ensure standardization of reading, the readers attended a joint training session using cases coming from the previous phase 2 studies. The readers then independently read a validation set where only the main endpoints (contrast score and overall diagnosis) were assessed. When validation results were judged to be satisfactory, readers were allowed to start the readings.

Statistical methods

The pre- to post-injection change in contrast score will be used as the **primary endpoint** in the non-inferiority analysis.

Linear mixed models analysis of variance with repeated measures will be performed on the pre to post-injection change in contrast score. Fixed effects are treatment, reader and treatment x reader interaction; patient effects are treated as random. The pre-injection contrast score was included in the model as a covariate in case of a strong correlation between with change and pre-treatment contrast score. A one-sided lower 97.5% confidence bound was calculated on the difference in change from baseline between OptiMARK and Magnevist.

Main **secondary efficacy analyses** concerned a comparison of sensitivity, specificity and diagnostic accuracy. The statistical analyses will use a generalized, linear mixed model approach that accommodates repeated correlated measurements on a binary endpoint and will incorporate the

binomial probability error distribution with the log it link function. This approach allows a unified and comprehensive analysis of diagnostic and diagnostic accuracy scores from all readers simultaneously.

The **non-inferiority margin** of $\Delta = -0.50$ is supported by data from the Summary Basis of Approval for Magnevist indicating that the mean difference between Magnevist and Placebo in pre- to post-injection Contrast Scores was between 1.00 and 1.34 which is one-half of 0.5 points.

RESULTS

CNS studies

Participant flow

Due to the role of the different imaging sequences in the assessment of the radiological parameters, two intent-to-treat (ITT) populations were defined for the re-read:
The ITT1 set was defined as patients who have received treatment after randomization with a MRI exam performed, and having at least the T1 pre-contrast sequence available for the reading. The ITT2 set was defined as a sub-set of ITT1 patients having T2 sequence available for the reading.
A per protocol (PP) population was defined as ITT1 patients for whom no major protocol deviation to the imaging protocol has been identified (PP1). No PP2 population was defined.
A first list of major deviations to the imaging protocol included a T1 post-contrast sequence not available for the reading andT1 post-contrast sequence available for the reading but not acquired according to the imaging protocol.

Conduct of the study

One patient presented a major deviation to the imaging protocol as the T1 post-contrast sequence was not acquired according to the imaging protocol.

Baseline data

There were no statistically significant differences between treatment groups with respect to the demographic characteristics age, sex, race, height, weight and BSA.

Numbers analysed

A total of 403 patients were enrolled in the 2 CNS studies; 265 were randomized to receive OptiMARK and 136 were randomized to receive Magnevist. In each treatment group, 3 patients were withdrawn prior to dosing. A total of 395 patients were dosed and included in the combined re-read population.

Patient disposition in CNS studies.

	OptiMARK®	Magnevist®	All
Number of patients enrolled	-	-	403
Number of patients randomized	265	136	401
Number of patients Discontinued Before Dosing	3 (1.1%)	3 (2.2%)	6 (1.5%)
Number of Patients Discontinued After Dosing	0 (0%)	0 (0%)	0 (0%)
Number of Patients Re-read	262 (98.9%)	133 (97.8%)	395 (98.5%)

Outcomes and estimation

The Primary Efficacy Endpoint, the mean difference in change in contrast score as assessed from pre to post-contrast images between OptiMARK and Magnevist was -0.018 ± 0.061. The lower bound of

the two-sided 95% CI (-0.14) for this difference was superior to the pre-defined non-inferiority margin (Δ = -0.5).
There was no significant treatment-by-reader interaction effect on the primary efficacy endpoint. There was a significant reader effect♦ (p<0.0001). Results are summarized in the following table.

Change in contrast score PRCF as assessed from pre- to post-contrast Images - ITT1 Population

Contrast score PRCF	Reading Pre		Reading Post		Variation Post - Pre		Non Inferiority Test°	
	OptiMARK	Magnevist	OptiMARK	Magnevist	OptiMARK	Magnevist		
	Number of patients N=258	Number of patients N=132	Number of patients N=258	Number of patients N=132	Number of patients N=258	Number of patients N=132		
All Readers								
Number of lesions	905	406	970	469	626	308	OptiMARK - Magnevist: Mean (SE) =	-0.018 (0.061)
Mean (Std)	1.58 (0.65)	1.60 (0.65)	2.22 (0.76)	2.28 (0.74)	0.63 (0.74)	0.66 (0.76)	Pr > |t| =	0.7667
Median	2.00	2.00	2.00	2.00	1.00	1.00	95% CI:	-0.14 ; 0.10
Min / Max	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	-1.0 / 3.0	-1.0 / 3.0	Non inferiority margin:	-0.50
							Treatment: Pr>F =	0.7667
							Reader: Pr>F =	<.0001
							Treatment x Reader: Pr>F =	0.9842

PRCF Statistics

Pre Reading Carried Forward procedure applied in 0.0% of lesions in post-reading.

° Change in contrast score PRCF as assessed from Pre to Post contrast images = Treatment + Reader + Treatment x Reader, repeated Reader / subject=Lesion(Patient) type=CS

Analysis on the ITT1 population with the sub-set of lesions with qualitative contrast enhancement♦:
The mean difference in change in contrast score as assessed from pre to post-contrast images between OptiMARK and Magnevist was -0.003 ± 0.089. The lower bound of the two-sided 95% CI (-0.18) for this difference was superior to the predefined non-inferiority margin (Δ=- 0.5). Therefore, it can be concluded that OptiMARK is not inferior to Magnevist with respect to the change in contrast score in the sub-set of lesions. There was no significant reader and treatment-by-reader interaction effect on the primary efficacy endpoint in the sub-set of lesions. Results are summarized in the following table.

♦ three blinded readers assessed the same set of images and the reader effect examines the inter-reader variability.

♦ For each lesion, presence of contrast enhancement was evaluated by the expert of concordance by comparing pre and post-contrast images and answering a yes/no question

Change in contrast score PRCF as assessed from pre to post-contrast images - description - ITT1 and LCE# Population

Contrast score PRCF	Reading Pre		Reading Post		Variation Post - Pre		Non Inferiority Test°	
	OptiMARK	Magnevist	OptiMARK	Magnevist	OptiMARK	Magnevist		
	Number of patients N=258	Number of patients N=132	Number of patients N=258	Number of patients N=132	Number of patients N=258	Number of patients N=132		
All Readers								
Number of lesions	359	171	506	247	301	154	OptiMARK - Magnevist: Mean (SE) =	-0.003 (0.089)
Mean (Std)	1.54 (0.61)	1.59 (0.61)	2.50 (0.64)	2.53 (0.57)	0.98 (0.75)	0.97 (0.75)	Pr > T =	0.9768
Median	2.00	2.00	3.00	3.00	1.00	1.00	95% CI:	-0.18 ; 0.17
Min / Max	0.0 / 3.0	0.0 / 3.0	1.0 / 3.0	1.0 / 3.0	-1.0 / 3.0	-1.0 / 3.0	Non inferiority margin:	-0.50
							Treatment: Pr>F =	0.9768
							Reader: Pr>F =	0.2429
							Treatment x Reader: Pr>F =	0.6699
PRCF Statistics								
Pre Reading Carried Forward procedure applied in 0.0% of lesions in post-reading.								

LCE Lesion with qualitative Contrast Enhancement
° Change in contrast score PRCF as assessed from Pre to Post contrast images = Treatment + Reader + Treatment x Reader, repeated Reader / subject=Lesion (Patient) type=CS

Results of the analysis on the PP1 population were similar to those obtained for the ITT1 analysis since there was only one patient difference in the two populations.

Primary efficacy endpoint: change in contrast score as assessed from pre to post-contrast Images – CNS Studies

Contrast Score	Reading Pre		Reading Post		Variation Post-Pre		Test
	OptiMARK	Magnevist	OptiMARK	Magnevist	OptiMARK	Magnevist	
Study 525							
Mean (SD)	1.48 (0.63)	1.53 (0.61)	1.99 (0.76)	2.06 (0.75)	0.46 (0.73)	0.49 (0.74)	95% CI -0.20 ; 0.15
Median	1.00	2.00	2.00	2.00	0.00	0.00	
Min/Max	0.0 / 3.0	0.0 / 3.0	1.0 / 3.0	1.0 / 3.0	-1.0 / 3.0	-1.0 / 2.0	
Study 488							
Mean (SD)	1.70 (0,66)	1.69 (0.69)	2.52 (0.65)	2.53 (0.64)	0.82 (0.71)	0.83 (0.76)	95% CI -0.17 ; 0,15
Median	2.00	2.00	3.00	3.00	1.00	1.00	
Min/Max	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	-1.0 / 3.0	-1.0 / 3.0	
Pooled CNS Studies							
Mean (SD)	1.58 (0.65)	1.60 (0.65)	2.22 (0.76)	2.28 (0.74)	0.63 (0.74)	0.66 (0.76)	95% CI -0.14 ; 0.10
Median	2.00	2.00	2.00	2.00	1.00	1.00	
Min/Max	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	-1.0 / 3.0	-1.0 / 3.0	

Secondary Efficacy Endpoints:

Comparable results were observed for both OptiMARK and Magnevist in any of the measured secondary endpoints except in *assessability to characterize a lesion* (on pre+post-contrast images; p=0.018, but not observed on the post-contrast images).

There was a significant reading effect (i.e. difference between pre and post contrast) on sensitivity (patient characterization[1] and diagnosis[2]) specificity and accuracy (patient characterization) as shown in the following tables.

Sensitivity, specificity and accuracy for patient characterization - comparison between treatments - ITT1 Population

		Final Characterization of the Patient											
		Reading Pre				Reading Pre+Post				Reading Post			
Overall Characterization of the Patient		OptiMARK		Magnevist		OptiMARK		Magnevist		OptiMARK		Magnevist	
		Number of patients N=258		Number of patients N=132		Number of patients N=258		Number of patients N=132		Number of patients N=258		Number of patients N=132	
		Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.
All Readers[oooo]	OCP												
	Negative	596	82	320	22	560	41	306	13	570	42	309	10
	Positive	34	56	22	23	70	97	36	32	60	96	33	35
	Missing Data°	6		9		6		9		6		9	
	Sensitivity / Specificity	0.41 / 0.95		0.51 / 0.94		0.70 / 0.89		0.71 / 0.89		0.70 / 0.90		0.78 / 0.90	
	Accuracy	0.85		0.89		0.86		0.87		0.87		0.89	

Sensitivity[oo] on true disease FCP = 'Present' N = 549 records

Sources of variation	Pr > Chi
Treatment	0.1450
Reader	0.0201
Reading	<.0001

Specificity[ooo] on true disease FCP = 'Absent' N = 2916 records

Sources of variation	Pr > Chi
Treatment	0.8577
Reader	<.0001
Reading	<.0001

FCP: Final Characterization of the Patient
OCP: Overall Characterization of the Patient
Abs.: Absence, Pres.: Presence
° Unknown or Undefined
°° Sensitivity: OCP (Positive) = Treatment + Reader + Reading / dist=Binomial type3 wald, repeated subject=Patient / type=AR corrw
°°° Specificity: OCP (Negative) = Treatment + Reader + Reading / dist=Binomial type3 wald, repeated subject=Patient / type=AR corrw
°°°° Each patient was evaluated by the three readers ad therefore generated three records

[1] Based on the characteristic of malignant/non-malignant documented in the investigator's CRF (present/absent) and the Overall Characterization of the Patient (OCP) evaluated from the characterization of the lesions performed by the blinded readers (positive/negative).

[2] Based on the Final diagnosis documented in the investigator's CRF (present/absent) and the overall diagnosis evaluated by the blinded readers (positive/negative).

Sensitivity, specificity and accuracy for patient diagnosis -comparison between treatments - ITT2 Population

Overall Diagnosis		Final Diagnosis											
		Reading Pre				Reading Pre+Post				Reading Post			
		OptiMARK		Magnevist		OptiMARK		Magnevist		OptiMARK		Magnevist	
		Number of patients N=255		Number of patients N=131		Number of patients N=255		Number of patients N=131		Number of patients N=255		Number of patients N=131	
		Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.
All Readers[oooo] OD													
	Negative	87	355	39	171	93	295	37	139	92	299	38	151
	Positive	21	280	12	155	18	347	13	190	18	343	12	181
	Missing Data°	22		16		12		14		13		11	
	Sensitivity / Specificity	0.44 / 0.81		0.48 / 0.76		0.54 / 0.84		0.58 / 0.74		0.53 / 0.84		0.55 / 0.76	
	Accuracy	0.49		0.51		0.58		0.60		0.58		0.57	

Sensitivity[oo] on true disease FD = 'Present' N = 2906 records

Sources of variation	Pr > Chi
Treatment	0.6723
Reader	0.0066
Reading	<.0001

Specificity[ooo] on true disease FD = 'Absent' N = 480 records

Sources of variation	Pr > Chi
Treatment	0.4353
Reader	0.0171
Reading	0.9083

FD: Final Diagnosis
OD: Overall Diagnosis
Abs.: Absence, Pres.: Presence
° Unknown or Undefined
°° Sensitivity: OD (Positive) = Treatment + Reader + Reading / dist=Binomial type3 wald, repeated subject=Patient / type=AR corrw
°°° Specificity: OD (Negative) = Treatment + Reader + Reading / dist=Binomial type3 wald, repeated subject=Patient / type=AR corrw
°°°° Each patient was evaluated by the three readers ad therefore generated three records

Regarding the nature of the first diagnosis (grouped by diagnosis classes), the percentage of non-specific lesions tended to decrease in both treatment groups from pre (23.5% and 24.1%) to pre+post (15.1% and 14.8%) and post-contrast images (16.1% and 18.6%) in OptiMARK and Magnevist group, respectively for all readers combined.

A significant reader effect was noted on the following secondary endpoints: change in contrast score as assessed from pre to pre+post contrast images, sensitivity and specificity for both patient characterization and diagnosis, accuracy for patient diagnosis, change in first diagnosis confidence score as assessed from pre to post-contrast images, and change in overall diagnosis confidence score as assessed from pre to pre+post-contrast images.

For both studies, inter-reader variability for contrast scores ranged from 37.4% to 65.5% (kappa ranging from 0.059 – 0.654). While inter-reader variability for the overall diagnosis ranged from 60.6% 70.7% (kappa: 0.536 – 0.64).

For both studies, intra-reader variability among repetitions for the contrast scores ranged from 64.0 % to 93.1% (kappa ranging from 0.567-0.919).

Liver studies

Participant flow

The efficacy analyses were performed on the ITT1, PP1 and ITT2 populations (see CNS studies). One patient was excluded from the ITT1 and ITT2 populations because no T1 pre-contrast images were available. Ten patients were excluded from the PP1 population: 6 patients because they did not receive the correct dose of contrast agent, 2 patients because the T1 post-contrast sequences were incomplete, 1 patient because T1 sequences were not acquired according to the imaging protocol and 1 patient because the T1 pre-contrast images were not available (corresponding to the patient excluded from the ITT1 and ITT2 populations).

Conduct of the study

Among the patients included in the ITT1 population, nine patients presented a major deviation to the imaging protocol. Six patients did not receive the correct dose of contrast agent, two patients had the T1 post-contrast sequences not acquired according to the imaging protocol and one patient had an incomplete set of post-contrast T1 sequences acquired

Baseline data

There were no statistically significant differences between treatment groups with respect to the demographic characteristics age, sex, race, height, weight and BSA.

Numbers analysed

A total of 410 patients were enrolled in the 2 liver studies; 202 were randomized to receive OptiMARK and 201 were randomized to receive Magnevist. Three patients were withdrawn prior to dosing in the OptiMARK group. Five patients were withdrawn prior to dosing in the Magnevist group. A total of 395 patients were dosed and included in the combined re-read population (table E11).

Patient disposition in liver studies.

	OptiMARK®	Magnevist®	All
Number of patients enrolled	-	-	410
Number of patients randomized	202	201	403
Number of patients Discontinued Before Dosing	3 (1.5%)	5 (2.5%)	8 (2.0%)
Number of Patients Discontinued After Dosing	0 (0%)	0 (0%)	0 (0%)
Number of Patients Re-read	199 (98.5%)	196 (97.5%)	395 (98.0%)

Outcomes and estimation

The primary efficacy endpoint, the mean difference in change in contrast score as assessed from pre to post-contrast images between OptiMARK and Magnevist was 0.013 ± 0.049. The lower bound of the two-sided 95% CI (-0.08) for this difference was superior to the pre-defined non-inferiority margin (Δ=- 0.5), demonstrating that OptiMARK is not inferior to Magnevist with respect to the change in contrast score as assessed from pre to post-contrast images. There was no significant treatment effect on mean changes in contrast score as assessed from pre to post-contrast images for the OptiMARK and Magnevist groups that were comparable: 0.38 ± 0.79 and 0.38 ± 0.72 respectively, indicating a significant increase in contrast scores following the administration of the contrast agents and demonstrating the efficacy of both contrast agents.
Mean contrast scores on post-contrast images for the OptiMARK and Magnevist groups were comparable: 2.17 ± 0.75 and 2.17 ± 0.74, respectively, corresponding to a contrast score slightly above grade 2 (good). There was no significant treatment-by-reader interaction effect on the primary

efficacy endpoint. There was a significant reader effect (p<0.0001). Results are summarized in the following table.

Change in contrast score PRCF as assessed from pre to post-contrast Images - ITT1 Population.

Contrast score PRCF	Reading Pre		Reading Post		Variation Post - Pre		Non Inferiority Test°	
	OptiMARK	Magnevist	OptiMARK	Magnevist	OptiMARK	Magnevist		
	Number of patients N=198	Number of patients N=196	Number of patients N=198	Number of patients N=196	Number of patients N=198	Number of patients N=196		
All Readers								
Number of lesions	957	959	1049	1037	721	726	OptiMARK - Magnevist: Mean (SE) =	0.013 (0.049)
Mean (Std)	1.82 (0.78)	1.82 (0.82)	2.17 (0.75)	2.17 (0.74)	0.38 (0.79)	0.38 (0.72)	Pr > T =	0.7936
Median	2.00	2.00	2.00	2.00	0.00	0.00	95% CI:	-0.08 ; 0.11
Min / Max	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	-2.0 / 3.0	-1.5 / 3.0	Non inferiority margin:	-0.50
							Treatment: Pr>F =	0.7936
							Reader: Pr>F =	<.0001
							Treatment x Reader: Pr>F =	0.8535

PRCF Statistics

Pre Reading Carried Forward procedure applied in 0.0% of lesions in post-reading.

° Change in contrast score PRCF as assessed from Pre to Post contrast images = Treatment + Reader + Treatment x Reader, repeated Reader / subject=Lesion (Patient) type=CS

Analysis on the ITT1 population with the sub-set of lesions with qualitative contrast enhancement:
The mean difference in change in contrast score as assessed from pre to post-contrast images between OptiMARK and Magnevist was -0.050 ± 0.069. The lower bound of the two-sided 95% CI (-0.19) for this difference was superior to the predefined non-inferiority margin (Δ = -0.5) showing that OptiMARK is not inferior to Magnevist with respect to the change in contrast score as assessed from pre to post-contrast images in the subset of lesions with qualitative contrast enhancement (following table).

Change in contrast score PRCF as assessed from pre to post contrast images - - ITT1 and LCE# Population

Contrast score PRCF	Reading Pre		Reading Post		Variation Post - Pre		Non Inferiority Test°	
	OptiMARK	Magnevist	OptiMARK	Magnevist	OptiMARK	Magnevist		
	Number of patients N=198	Number of patients N=196	Number of patients N=198	Number of patients N=196	Number of patients N=198	Number of patients N=196		
All Readers								
Number of lesions	566	540	606	599	455	456	OptiMARK - Magnevist: Mean (SE) =	-0.050 (0.069)
Mean (Std)	1.79 (0.75)	1.81 (0.80)	2.10 (0.71)	2.11 (0.72)	0.34 (0.82)	0.38 (0.77)	Pr > T =	0.4695
Median	2.00	2.00	2.00	2.00	0.00	0.00	95% CI:	-0.19 ; 0.09
Min / Max	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	-2.0 / 3.0	-1.5 / 3.0	Non inferiority margin:	-0.50
							Treatment: Pr>F =	0.4695
							Reader: Pr>F =	<.0001
							Treatment x Reader: Pr>F =	0.1702
PRCF Statistics								
Pre Reading Carried Forward procedure applied in 0.0% of lesions in post-reading.								

LCE Lesion with Qualitative Contrast Enhancement
° Change in contrast score PRCF as assessed from Pre to Post contrast images = Treatment + Reader + Treatment x Reader, repeated Reader / subject=Lesion (Patient) type=CS

The results were similar for the PP1 population.

Primary efficacy endpoint: change in contrast score as assessed from pre to post-contrast Images – Liver Studies (490/526)

Contrast Score	Reading Pre		Reading Post		Variation Post-Pre		Test
	OptiMARK	Magnevist	OptiMARK	Magnevist	OptiMARK	Magnevist	
Study 526							
Mean (SD)	1.83 (0.86)	1.80 (0.86)	2.21 (0.76)	2.15 (0.75)	0.41 (0.80)	0.36 (0.76)	95 % CI -0.06 ; 0.21
Median	2.00	2.00	2.00	2.00	0.00	0.00	
Min/Max	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	-2.0 / 3.0	-1.5 / 3.0	
Study 490							
Mean (SD)	1.81 (0.68)	1.85 (0.74)	2.13 (0.74)	2.19 (0.74)	0.35 (0.77)	0.40 (0.66)	95 %CI -0.17 ; 0.09
Median	2.00	2.00	2.00	2.00	0.00	0.00	
Min/Max	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	1.0 / 3.0	-2.0 / 2.0	-1.0 / 2.0	
Pooled Liver Studies							
Mean (SD)	1.82 (0.78)	1.82 (0.82)	2.17 (0.75)	2.17 (0.74)	0.38 (0.79)	0.38 (0.72)	95 %CI -0.08 ; 0.11
Median	2.00	2.00	2.00	2.00	0.00	0.00	
Min/Max	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	0.0 / 3.0	-2.0 / 3.0	-1.5 / 3.0	

Analysis of the results of the **secondary efficacy endpoints** show that OptiMARK and Magnevist *performed comparably* in the measured secondary endpoints except on the relative variation of signal intensity at lesion level for portal phase images (82.55±129.35 and 57.59±61.37 respectively; p=0.0258) and delayed phase (86.3±118.65 and 63.51±75.75 respectively; p=0.0381).

A significant reading effect (difference between pre and post contrast) was observed for sensitivity (for patient characterization[3] or diagnosis[4]) and accuracy for patient diagnosis but not for specificity (following tables).

Sensitivity, specificity and accuracy for patient characterization - comparison between treatments - ITT1 Population

Overall Characterization of the Patient		Final Characterization of the Patient											
		Reading Pre				Reading Pre+Post				Reading Post			
		OptiMARK		Magnevist		OptiMARK		Magnevist		OptiMARK		Magnevist	
		Number of patients N=198		Number of patients N=196		Number of patients N=198		Number of patients N=196		Number of patients N=198		Number of patients N=196	
		Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.
All Readers°°°° OCP													
	Negative	338	117	321	123	327	67	318	65	328	71	318	71
	Positive	19	102	24	108	30	152	27	166	29	148	27	160
	Missing Data°	18		12		18		12		18		12	
	Sensitivity / Specificity	0.47 / 0.95		0.47 / 0.93		0.69 / 0.92		0.72 / 0.92		0.68 / 0.92		0.69 / 0.92	
	Accuracy	0.76		0.74		0.83		0.84		0.83		0.83	

Sensitivity°° on true disease FCP = 'Present' N = 1350 records

	Sources of variation	Pr > Chi
	Treatment	0.9599
	Reader	<.0001
	Reading	<.0001

Specificity°°° on true disease FCP = 'Absent' N = 2106 records

	Sources of variation	Pr > Chi
	Treatment	0.7966
	Reader	0.0002
	Reading	0.0437

FCP: Final Characterization of the Patient
OCP: Overall Characterization of the Patient
Abs.: Absence, Pres.: Presence
° Unknown or Undefined
°° Sensitivity: OCP (Positive) = Treatment + Reader + Reading / dist=Binomial type3 wald, repeated subject=Patient / type=AR corrw
°°° Specificity: OCP (Negative) = Treatment + Reader + Reading / dist=Binomial type3 wald, repeated subject=Patient / type=AR corrw
°°°°Each patient was evaluated by the three readers and therefore generated three records

[3] Based on the characteristic of malignant/non-malignant documented in the investigator's CRF (present/absent) and the Overall Characterization of the Patient (OCP) evaluated from the characterization of the lesions performed by the blinded readers positive/negative).
[4] Based on the Final diagnosis documented in the investigator's CRF (present/absent) and the overall diagnosis evaluated by the blinded readers (positive/negative).

Sensitivity, specificity and accuracy for patient diagnosis -comparison between treatments - ITT2 Population

Overall Diagnosis		Final Diagnosis											
		Reading Pre				Reading Pre+Post				Reading Post			
		OptiMARK		Magnevist		OptiMARK		Magnevist		OptiMARK		Magnevist	
		Number of patients N=198		Number of patients N=196		Number of patients N=198		Number of patients N=196		Number of patients N=198		Number of patients N=196	
		Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.	Abs.	Pres.
All Readers[oooo] OD													
	Negative	17	183	19	198	22	170	21	161	21	173	21	171
	Positive	2	244	3	251	5	348	3	357	5	342	2	350
	Missing Data°	148		117		49		46		53		44	
	Sensitivity / Specificity	0.57 / 0.89		0.56 / 0.86		0.67 / 0.81		0.69 / 0.88		0.66 / 0.81		0.67 / 0.91	
	Accuracy	0.59		0.57		0.68		0.70		0.67		0.68	

Sensitivity[oo] on true disease FD = 'Present' N = 2948 records	
Sources of variation	Pr > Chi
Treatment	0.9971
Reader	<.0001
Reading	<.0001

Specificity[ooo] on true disease FD = 'Absent' N = 141 records	
Sources of variation	Pr > Chi
Treatment	0.9157
Reader	<.0001
Reading	0.9704

FD: Final Diagnosis
OD: Overall Diagnosis
Abs.: Absence, Pres.: Presence
° Unknown or Undefined
°° Sensitivity: OD (Positive) = Treatment + Reader + Reading / dist=Binomial type3 wald, repeated subject=Patient / type=AR corrw
°°° Specificity: OD (Negative) = Treatment + Reader + Reading / dist=Binomial type3 wald, repeated subject=Patient / type=AR corrw
°°°° Each patient was evaluated by the three readers and therefore generated three records

Regarding the nature of the first diagnosis for the ITT1 population (grouped by diagnosis classes), the percentage of non-specific lesions decreased in both treatment groups from pre (65.8% and 63.0%) to pre+post (16.5% and 15.4%) and post-contrast images (17.7% and 18.2%) in OptiMARK and Magnevist group, respectively for all readers combined.

There was a significant reader effect in change in contrast score as assessed from pre to pre+post contrast images, sensitivity and specificity for patient characterization and diagnosis, accuracy for patient diagnosis and change in first diagnosis score as assessed from pre to post-contrast images.

In both studies, inter-reader variability in contrast scores ranged from 45.7 % to 73.1 % (kappa: 0.233 – 0.532). While agreement among readers for the overall diagnosis ranged from 64.4% to 73.1 % (kappa: 0.512 – 0.631).

In both studies, intra-reader variability in contrast score evaluation ranged from 62.0% to 90.2% (kappa: 0.478- 0.858).

- Clinical studies in paediatric populations

Study 552 was an open-label, single-centre, phase 1 study to evaluate the pharmacokinetics and safety of OptiMARK in seventeen healthy paediatric subjects (2-18 years), dosed with 0.1 mmol/kg OptiMARK and followed up for 72 hours.

Study 597 was an open-label, single-dose phase 4, multicentre (n = 10) study conducted in the USA. The objective of the study was to evaluate the safety, efficacy, and pharmacokinetic profile of OptiMARK in paediatric patients referred for MRI of the liver or CNS. Patients were stratified by age to one of two groups (2 to 11 and 12 to 18 years of age) and all patients were to receive a single intravenous injection of OptiMARK at a dose of 0.1 mmol/kg. A total of 100 patients were dosed. Serial blood and pooled urine samples were collected from a subgroup of 30 patients (17 patients 2 thru 11 years of age and 13 patients 12 thru 18 years of age) for pharmacokinetic analysis.

The primary efficacy endpoints included the degree of Confidence in Diagnosis (CD) and Level of Conspicuity (LC) for lesion visualisation as determined by the investigator and independent blinded readers. Accuracy, sensitivity and specificity were also analysed as primary efficacy endpoints.

Secondary efficacy endpoints included the overall differences between the pre- and post-contrast Gray Scale Pixel (GSP) statistics for each lesion, the Receiver Operating Characteristic (ROC) used to assess the sensitivity and specificity of the imaging test, and the ability to characterise the lesion area from parenchyma/structures based on both pre-contrast and combined pre-contrast and post-contrast images scored.

Additional secondary efficacy analyses included an assessment by the Principal Investigator on the changes in Confidence in Diagnosis (CD) and Level of Conspicuity (LC) for lesion visualization in the presence and absence of OptiMARK.

Efficacy results demonstrated that the administration of OptiMARK significantly increased the accuracy and sensitivity for blinded reviewers to detect the presence of a CNS lesion in the paediatric population of 2 through 18 years of age and significantly increased the level of lesion conspicuity, and confidence in diagnosis.

The Post-T1 images showed a significant increase in the intensity and the variability of the grey scale measurements for the lesion core. In addition, OptiMARK produced an increase in the intensity of the parenchyma grey scale signal but not the variability. Injection of OptiMARK caused no statistically significant change in the cross sectional area of the measured lesions. ROC curve analysis showed that the administration of OptiMARK significantly increased lesion conspicuity and increased accuracy for making a correct diagnosis. The same analysis showed that OptiMARK had little effect on confidence in diagnosis when evaluated under totally blinded conditions.

- Discussion on clinical efficacy

The currently presented studies are re-reads of the original studies following the scientific advice of the CHMP in 2005. Two studies support the CNS indication (488 and 525) and 2 studies the liver indication (490 and 526).

The 4 pivotal studies shared the same design, being multi-centre, randomized, double-blind, non-inferiority studies to evaluate the safety, tolerance, and efficacy of OptiMARK compared to Magnevist in CNS or liver lesion. No major differences in patient demographics or basic characteristics were noted.

In the two pivotal CNS studies the Primary Efficacy Endpoint, the mean difference in change in contrast score as assessed from pre to post-contrast images between OptiMARK and Magnevist was -0.018 ± 0.061. The lower bound of the two-sided 95% CI (-0.14) for this difference was superior to the pre-defined non-inferiority margin (Δ = -0.5) demonstrating that OptiMARK is not inferior to Magnevist with respect to the change in contrast score

In the two pivotal liver studies the mean difference in change in contrast score as assessed from pre to post-contrast images between OptiMARK and Magnevist was 0.013 ± 0.049. The lower bound of the two-sided 95% CI (-0.08) for this difference was superior to the pre-defined non-inferiority margin (Δ=- 0.5), demonstrating that OptiMARK is not inferior to Magnevist with respect to the change in contrast score as assessed from pre to post-contrast images.

Analysis of multiple secondary endpoints like sensitivity, specificity and accuracy showed a comparable performance between OptiMARK and Magnevist.

Clinical safety

All of the twenty-six studies included in the clinical development program of OptiMARK are included in the Summary of Clinical Safety of the present application. Seven of these studies were performed since the initial MAA was withdrawn in 1999 due to CPMP concerns – 4 Phase 2 studies and 3 Phase 4 studies. Of the 26 studies, 4 were pharmacokinetic studies, 1 was a pharmacodynamic study, 4 evaluated efficacy and safety in subjects with CNS and liver pathology, 15 were designed to evaluate safety, 1 was a safety and pharmacokinetic study and 1 evaluated safety, efficacy and pharmacokinetics.

- Patient exposure

In the clinical development program, a total of 2752 injections of OptiMARK were administered in 2398 subjects, 137 subjects were exposed to placebo, and 475 subjects were exposed to three other gadolinium-containing MRI contrast agents used as active comparators (Magnevist, Omniscan, and ProHance). The demographics of the studied population are summarized in the following table.

Summary for demographic information for OptiMARK combined, comparators combined, and placebo subject/patients. Safety population

		All OptiMARK™ Combined	Placebo	Active comparators Combined
N		2752[a]	137[a]	475[a]
Age (years)	Mean ± SD	48.07 ± 16.73	40.18 ± 16.16	49.03 ± 15.65
	Range	1.16 – 88.00	18.00 – 78.00	18.00 – 88.00
Age Categories (years)	<18	117 (4.25%)	0 (0.00%)	0 (0.00%)
	18 – 40	693 (25.18%)	73 (53.28%)	149 (31.37%)
	40 – 65	1519 (55.20%)	50 (36.50%)	239 (50.32%)
	>65	423 (15.37%)	14 (10.22%)	87 (18.32%)
Sex, n (%)	Female	1222 (44.40%)	58 (42.34%)	254 (53.47%)
	Male	1530 (55.60%)	79 (57.66%)	221 (46.53%)
Race, n (%)	White	2321 (84.34%)	108 (78.83%)	383 (80.63%)
	Black	266 (9.67%)	20 (14.60%)	63 (13.26%)
	Asian	58 (2.11%)	4 (2.92%)	14 (2.95%)
	Other	107 (3.89%)	5 (3.65%)	15 (3.16%)

SD = standard deviation

OptiMARK was administered in all 26 studies. Placebo (saline) was administered in Studies 433, 489, 716, and 717. Studies with active comparators were: Magnevist (Studies 488, 490, 525, 526, 555, 716, and 789); ProHance and Omniscan (Study 789), 789), which was a crossover study. Therefore, the 26 subjects who received ProHance are the same 26 subjects who received Omniscan. Each of those 26 subjects also received Magnevist in the study and are included in the Magnevist treatment group. Magnevist was also administered in Studies 488, 490, 525, 526, 555, and 716.

In the Phase 3 pivotal studies, a total of 262 subjects with CNS indications and 199 subjects with liver indications received OptiMARK. All studies investigating other indications, safety, and pharmacokinetics, although not pertinent to the CNS or liver indication are also included for the global safety assessment of OptiMARK.

- Adverse events

Among the 3364 subjects who participated in all phases of the clinical development of OptiMARK, the overall incidence of AEs was comparable in subjects receiving OptiMARK (757/2752, 27.5%) compared with 30.1% (143/475) in the active comparator group, and 36.5% (50/137) in subjects who received placebo. Overall, more females had AEs than did males (34.3% compared with 23.0%) and each of the common AEs was reported by more females than males with the exception of dizziness. The proportion of subjects with any AE was similar for both white and non-white racial subgroups

(26.9% for non-whites compared with 28.4% for whites). Overall, no trend was observed with respect to race for any AE.
The most common AE in the combined OptiMARK group were headache (5.5%), dysgeusia (4.0%), feeling hot (3.9%), dizziness (2.4%), nausea (2.0%), and diarrhoea (1.2%). Only 1 of these, feeling hot, occurred more often in subjects treated with OptiMARK versus placebo. Other commonly reported AEs occurred at a similar frequency in the OptiMARK versus the comparator group.

The following drug-related events have been reported from clinical trials and from post-marketing use of OptiMARK:

System Organ Class (MedDRA)	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1,000, <1/100)**	**Rare (≥1/10,000, <1/1,000)**	**Very Rare (<1/10,000)**
Immune System Disorders		Anaphylactic reaction		
Metabolism and Nutrition Disorders			Decreased appetite	
Psychiatric Disorders			Anxiety, Sleep disorder	Confusional state
Nervous System Disorders	Dizziness, Headaches, Dysgeusia	Hypoaesthesia, Paraesthesia, Parosmia	Syncope, Tremor, Somnolence, Burning sensation	Convulsion
Eye Disorders			Erythema of eyelid, Eye pain, Vision blurred	Ocular hyperaemia
Ear and Labyrinth Disorders			Tinnitus	
Cardiac Disorders			Tachycardia, Palpitations, AV block first degree, Extrasystoles	Arrhythmia
Vascular Disorders		Flushing	Hypotension, Hypertension	
Respiratory, Thoracic and Mediastinal Disorders		Nasal congestion, Throat irritation	Dyspnoea, Dysphonia, Cough, Rhinorrhoea, Throat tightness	Bronchospasm, Pharyngeal oedema, Pharyngitis, Rhinitis, Sneezing
Gastrointestinal Disorders		Nausea, Diarrhoea	Salivary hypersecretion,, Vomiting, Abdominal pain, Constipation, Dry mouth	
Skin and Subcutaneous Tissue Disorders		Urticaria, Pruritus, Rash	Cold sweat, Erythema, Hyperhidrosis	Periorbital oedema
Renal and Urinary Disorders			Blood creatinine increased, Hematuria	
General Disorders and Administration Site Conditions	Feeling hot	Chest discomfort, Feeling cold, Administration site reactions	Pain, Chest pain, Face oedema, Fatigue, Fever, Oedema peripheral, Peripheral coldness	Malaise, Feeling abnormal,

System Organ Class (MedDRA)	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)	Very Rare (<1/10,000)
Investigations			ALT increased, Urine analysis abnormal, Urine electrolytes abnormal CPK Increased, Haemoglobin decreased, Blood calcium abnormal	Electrocardiogram QT prolonged

*Medical Dictionary for Regulatory Activities

- Serious adverse event/deaths/other significant events

Eighteen subjects experienced serious adverse events while enrolled in an OptiMARK clinical studies. All serious adverse events were considered by the Investigator to be unrelated to the administration of the study drug except one case. There was no evidence of an increase in serious adverse events in any body system or of a relationship to dose.
The reported case of serious AE was case of anaphylactic reaction in a female patient administered 0.1 mmol/kg OptiMARK. The patient was known to have a prior adverse reaction to iodinated contrast agent, but had never received gadolinium contrast agents for a MRI. The patient recovered after treatment.

One death occurred during the clinical studies of OptiMARK. A 45 years old AIDS patient receiving a single dose of OptiMARK 0.1 mmol/kg, died within 3 days of study participation. The Investigator did not consider the death related to OptiMARK and the FDA was notified.
In addition, the Sponsor was notified of the deaths of 7 subjects subsequent to their participation in the OptiMARK clinical development program. None of the deaths of subjects exposed to OptiMARK occurred within less than 1weeks from study participation, and none was considered related to study drug.

- Laboratory findings

Mean changes between baseline and all post-baseline values were small for most haematology and clinical chemistry laboratory parameters, and were comparable in the 'All OptiMARK Combined', placebo, and Magnevist groups. Total iron binding capacity (TIBC-AA) increased for the OptiMARK-treated subjects after the injection, but returned to close to baseline values within 24 hours of the injection. Serum zinc values decreased after injection, returning to the normal range by 24 hours post-injection.
Mean changes between baseline and all post-baseline values were small for most urinalysis laboratory parameters, and were comparable in the All OptiMARK Combined, placebo, and Magnevist groups, with the exception of zinc levels, which increased shortly after the injection for those subjects receiving OptiMARK, and returned to the normal range by 48 hours.

No clinically significant changes were noted for either of the target patient populations with CNS or liver pathology.
No clinically significant trends or changes in vital signs occurred by treatment group or dose group.
No clinically significant trends or changes in ECG measurements occurred by treatment or dose group.

- Safety in special populations

No trend was observed with respect to race for any AE.
With respect to AEs reported for > 1% of subjects of either sex who received OptiMARK 0.1 mmol/kg in any study, overall, more females had AEs than did males (34.3% compared with 23.0%, respectively, a difference of approximately 10% overall).
Among the 3 adult subgroups, the proportions of subjects reporting each common AE were similar, and none of the AEs appeared to increase with increasing age. The AE profile for the youngest age

subgroup appears to be qualitatively different. No subject in the youngest age subgroup experienced headache, dysgeusia, dizziness, or feeling hot, which were 4 of the 5 most commonly reported AEs for the adults. The incidences of nausea, diarrhoea, vomiting, injection site reaction, and prolonged electrocardiogram QT were similar among all the age subgroups.

- Safety related to drug-drug interactions and other interactions

Drug interactions with other contrast agents or other drugs were not studied.

- Discontinuation due to adverse events

Discontinuations for adverse events were reported for 3 subjects (2 OptiMARK, 1 Magnevist) who received at least 1 dose of study drug that were either unrelated or unlikely to have been related to the study drug. In addition, 12 subjects were identified in review of final clinical study reports to have discontinued prior to receiving treatment. Investigators assessed each of these adverse events as unrelated to study drug.

- Post marketing experience

A post-marketing safety report for the period from the launch of OptiMARK in the year 2000 (United States) to 31 December 2005 was provided in the current application. Furthermore, additional post-marketing safety data covering the period until December 2006 have been submitted. As of December 2006, more than 4.4 million doses of OptiMARK have been administered to patients, worldwide. OptiMARK is distributed in containers for single use. Hence, it is estimated that on average the number of units sold throughout the report period equals the number of exposed subjects.

- Discussion on clinical safety

Among the 3364 subjects who participated in all phases of the clinical development of OptiMARK, the overall incidence of AEs was comparable in subjects receiving OptiMARK (27.5%) the active comparator group (Magnevist, Omniscan, and ProHance) (30.1%), and 36.5% in subjects who received placebo.

The most common AE in the combined OptiMARK group were headache (5.5%), dysgeusia (4.0%), feeling hot (3.9%), dizziness (2.4%), nausea (2.0%), and diarrhoea (1.2%). %). The reported AE are conforming to that known of similar gadolinium chelate diagnostic agents and these AE are reflected in section 4.8 of the SPC. The overall incidence of AEs increased in a dose-related manner in the OptiMARK treatment groups, but higher doses of OptiMARK were not associated with an increase in the severity of AEs. A special paediatric study was conducted in patients between 2 and 18 years and revealed no special AEs.

All serious adverse events were considered to be unrelated to the administration of the study drug except one case of anaphylaxis. The possibility of occurrence of anaphylaxis is documented in the SPC. Eight deaths were reported, but none was considered related to OptiMARK.

The recorded increase in QTc from baseline was between 5 and 15 msec using the 0.2 mmol/kg and 0.5 mmol/kg at 2 hours and immediately post injection respectively. No cases of ventricular arrhythmias were recorded using OptiMARK. These changes do not warrant concern regarding the effect of OptiMARK on QTc.

Important identified risks are the use of gadolinium in patients with kidney failure. Acute renal failure was reported after administration of gadolinium-based contrast agents in patients with moderate to severe chronic renal failure. Risk factors for ARF after gadolinium toxicity include diabetic nephropathy and low GFR (Ergun et al., 2006 et al).

Important missing safety information is about gadolinium-containing contrast agents and Nephrogenic Systemic Fibrosis or Nephrogenic Fibrosing Dermopathy (NSF/NFD) that occurs in patients with renal failure.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table Summary of the risk management plan

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Nephrogenic systemic fibrosis (NSF)	• Routine postmarketing surveillance • Initiation of a targeted questionnaire to be used by Pharmacovigilance personnel when taking a report of an adverse event that describes a cutaneous component resembling NSF/NFD. This questionnaire will focus on key historical points, such as gadolinium dosage, renal status, biopsy results, etc. Laboratory –based studies to try to understand the mechanism by which gadolinium provokes NSF	Routine: SmPC section 4.3 contains the following wording: "OptiMARK is contraindicated in patients with severe renal impairment (GFR <30ml/min/1.73m^2), and those who have had or are undergoing liver transplantation." SmPC section 4.4 contains the following wording: "Renal impairment and liver transplant patients There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with severe renal impairment (GFR <30ml/min/1.73m^2) and those who have had or are undergoing liver transplantation. Therefore OptiMARK should not be used in these populations (see section 4.3). Cases of NSF have also been reported in patients with moderate renal impairment (GFR <60ml/min/1.73m^2) with use of gadolinium-containing contrast agents. OptiMARK should be used in these patients with caution. Gadoversetamide is dialyzable. Haemodialysis shortly after OptiMARK administration in patients currently receiving haemodialysis may be useful at removing OptiMARK from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis." Information in section 5.2 of the SPC
Hypersensitivity reactions	• Routine pharmacovigilance	Contraindication in section 4.3 of the SPC: "Hypersensitivity to gadoversetamide or to any of the excipients or to other gadolinium containing products." Warning in section 4.4 of the SPC of hypersensitivity reactions Mention in section 4.8 of the SPC

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical

performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The primary pharmacodynamic effect of OptiMARK, a gadolinium chelate based MRI contrast agent, has been demonstrated by its effect on tissue proton relaxation times (T1 and T2) and impact on the clarity of the MRI image. Gadolinium chelates have already shown their therapeutic efficiency in the field of MRI. Pharmacodynamic studies presented have shown that the imaging effects of OptiMARK and Magnevist (a standard gadolinium chelate available in the market) are quantitatively equivalent.
The safety pharmacology studies clearly set out that effects on the QT interval are unlikely to occur. The effects of OptiMARK and other agents were mimicked by comparable increases in osmolarity produced by mannitol. These results suggest that OptiMARK caused prolongation of cardiac action potentials largely as a result of hypertonicity rather than specific ion-channel interactions. These *in vitro* effects were observed only at the highest concentration, which was at least 100x the maximum plasma concentration that would be achieved under conditions of clinical use. No significant effect on QT interval was noted either in the *in vivo* safety pharmacology studies that used of 10x doses in excess in the proposed clinical use.

Gadoversetamide, the active active substance in OptiMARK, appears to have an appropriate pharmacokinetic profile for its intended application as an extracellular magnetic resonance contrast agent. Gadoversetamide distributes between plasma and interstitial fluid, does not penetrate the blood-brain barrier, undergoes minimal passage of the placental barrier and is rapidly excreted in urine in unchanged form. It is known that the clearance of gadolinium-derivatives is highly delayed in patients with renal insufficiency therefore excretion might be a problem in this type of patients.
A low residual level of radioactivity (~ 0.2-0.3 % of the injected dose) in the rat skeleton was found to be constant over a 4-7 day interval after administration of Gd^{153} OptiMARK. Data for these studies were consistent with published reports showing residual radioactivity in the bones of rodents, days after administration of a single dose of Gd^{153} labelled commercial products. The absence of toxicological effects on bone makes this issue a minor concern.
No pharmacokinetic studies were carried out after repeated administration. Although the product is intended for single use only, data on repeated administration might be useful to support repeated dose toxicity studies.

Studies with OptiMARK did not elicit classical signs of single-dose gadolinium toxicity. There appears to be an effect on male reproduction that is permanent. There were still marked numbers of atrophic testicular tubules accompanied by minimal diffuse interstitial cell hyperplasia 8 and 19 weeks after dosing was stopped. No mature spermatozoa were seen in rats after 19 weeks recovery, only some slight reversibility in the small number of tubules where germinal epithelium survived. The effects on male reproduction have not been considered of clinical concern because the effects were not noted in single dose toxicity studies, and the intended clinical application is for one use only.
There is also a potential for serious adverse effects in foetal development. Increases in skeletal and visceral variations, some delays in the attainment of reflexes and increased prevalence of postural limb anomalies and of cardiovascular malformations have been described in rats and rabbits following repeated exposure to gadoversetamide. The threshold of adverse effects for the foetus appears to be below a clearly toxic level for the mother. The proposed indication involves a single administration and serious reproductive effects would not be anticipated, nonetheless, caution in the use of gadoversetamide in pregnant women is warranted and has been highlighted accordingly in the SPC.

Efficacy

The currently presented studies are a re-evaluation of the original studies following the scientific advice of the CHMP in 2005. Two studies support the CNS indication (study 488 and 525) and 2 studies the liver indication (study 490 and 526).
The 4 pivotal studies shared the same design of being: multicentre, randomized, double-blind, non-inferiority studies to evaluate the safety, tolerance, and efficacy of OptiMARK compared to

Magnevist in CNS or liver lesion. The primary endpoint was to demonstrate non-inferiority of OptiMARK versus Magnevist as assessed by the change in contrast score between pre and post-contrast images in CNS and liver studies.
The results of the individual studies as well as the pooled results show that the pre-defined primary endpoint of the non-inferiority of OptiMARK versus Magnevist with respect to the change in contrast score from pre- to post-contrast images was achieved. Analysis of multiple secondary endpoints endpoints including sensitivity, specificity and accuracy showed a comparable performance between OptiMARK and Magnevist.

Safety

The most common AE in the combined OptiMARK group were headache (5.5%), dysgeusia (4.0%), feeling hot (3.9%), dizziness (2.4%), nausea (2.0%), and diarrhoea (1.2%). %). The reported AE are conforming to that known of similar gadolinium chelate diagnostic agents and these AE are reflected in section 4.8 of the SPC. The overall incidence of AEs increased in a dose-related manner in the OptiMARK treatment groups, but higher doses of OptiMARK were not associated with an increase in the severity of AEs. A special paediatric study was conducted in patients between 2 and 18 years and revealed no special AEs.

All serious adverse events were considered to be unrelated to the administration of the study drug except one case of anaphylaxis. The possibility of occurrence of anaphylaxis is documented in the SPC. Eight deaths were reported, but none was considered related to OptiMARK.

Important identified risks are the use of gadolinium in patients with kidney failure. Acute renal failure was reported after administration of gadolinium-based contrast agents in patients with moderate to severe chronic renal failure. Risk factors for ARF after gadolinium toxicity include diabetic nephropathy and low GFR (Ergun et al., 2006 et al).

Important missing safety information is about gadolinium-containing contrast agents and Nephrogenic Systemic Fibrosis or Nephrogenic Fibrosing Dermopathy (NSF/NFD) that occurs in patients with renal failure.

Post-marketing experience did not reveal any new AE but was consistent with that reported with other gadolinium-based contrast agents.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

An appropriate test was conducted on behalf of the Applicant to assess the readability and usability of the Patient Information Leaflet (PIL) for OptiMARK 500 micromol/ml solution for injection in line with EU directive 2004/27/EC.
The PIL is regarded as having successfully passed the test with 90% of the subjects achieving greater than 90% correct answers in rounds 2 and 3, following amendments after round 1.
The final PIL (page 40 of the Readability testing document) is, therefore, acceptable for consideration for opinion.

Risk-benefit assessment

Results of the four pivotal studies as well as the pooled results show that the pre-defined primary endpoint of the non-inferiority of OptiMARK versus Magnevist with respect to the change in contrast score from pre- to post-contrast images was achieved. Analysis of multiple secondary endpoints endpoints like sensitivity, specificity and accuracy showed a comparable performance between OptiMARK and Magnevist. Overall the administration of OptiMARK is safe. Taking the safe use and

the evidence of demonstrated non-inferiority to Magnevist into account, the risk-benefit of OptiMARK in the claimed indication is positive.
A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

It should be emphasized that the chosen primary endpoints were measures of technical performance. According to the Ptc Diagnostic Agents CPMP/EWP/1119/98 the primary endpoints of efficacy should be measures of diagnostic performance. Future studies investigating similar products should be designed accordingly.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of OptiMARK in the diagnosis of focal lesions and abnormal structures in the CNS and liver in patients with known or highly suspected pathology was favourable and therefore recommended the granting of the marketing authorisation.