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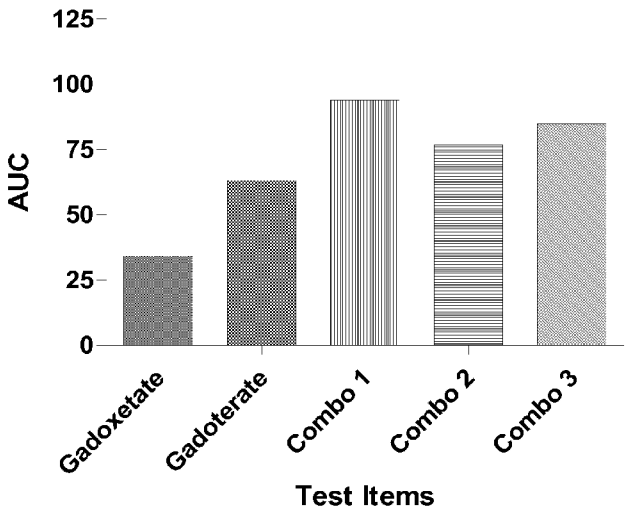
[Continued on next page]

(54) Title: FORMULATIONS COMPRISING A COMBINATION OF MRI CONTRAST AGENTS

Figure 4F



(57) Abstract: The present invention relates to in vivo imaging and in particular to magnetic resonance imaging (MRI). Provided by the present invention is a pharmaceutical formulation suitable for use in an MRI procedure and which offers advantages over known such formulations. A particular dose of the pharmaceutical formulation of the invention is also envisioned as well as the use of said dose in a method of in vivo imaging. This present invention provides for simultaneous administration of a liver specific agent and a second MR contrast agent that is capable of better/further enhancing the dynamic vascular phase in a patient. The method of the invention has the advantage of simplicity and patient comfort, compared to sequential injections. Furthermore, the method of the invention provides the advantage that it can enable a lower cumulative dose of contrast agents.

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FORMULATIONS COMPRISING A COMBINATION OF MRI CONTRAST AGENTS

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to *in vivo* imaging and in particular to magnetic resonance imaging (MRI). Provided by the present invention is a pharmaceutical formulation suitable for use in an MRI procedure and which offers advantages over other known such formulations. A particular dose of the pharmaceutical formulation of the invention is also envisioned as well as the use of said dose in a method of *in vivo* imaging.

DESCRIPTION OF RELATED ART

[0002] Gadoxetate (Gd-EOB-DTPA, Primovist in Europe and Eovist in the USA) is a liver-specific magnetic resonance imaging contrast agent that has up to 50% hepatobiliary excretion in the normal liver. After intravenous injection, gadoxetate distributes into the vascular and extravascular spaces and progressively into the hepatocytes and bile ducts during the arterial, portal venous and hepatobiliary phases. Gadoxetate behaves similarly to non-specific gadolinium chelates during the arterial and portal venous phases, and adds substantial information during the hepatobiliary phase, improving the detection and characterization of focal liver lesions and diffuse liver disease (Beers *et al* 2012 J Hepatol; 57(2): 421–429).

[0003] However, it is well recognized that gadoxetate suffers from an overall poor dynamic vascular phase (comprises arterial phase "AP", portal venous phase "PVP" and late venous phase "LVP") compared to non-specific gadolinium chelates (Frydrychowicz *et al* 2012 JMRI; 35(3): 492–511). Possible remedies to this include using higher doses of gadoxetate, slowing the rate of gadoxetate injection, or an additional injection of a general purpose (nonspecific) agent known to better enhance the dynamic vascular phase.

[0004] Zech et al. (2009 Investigat Radiol; 44(6): 305-310) evaluated a slow injection rate (or "bolus stretch") and demonstrated a favourable bolus shape with a standard clinical dose of gadoxetate. This bolus stretch compensates for the lower gadolinium amount in the single dose of gadoxetate with a potential improvement in the AP at the early part of the dynamic vascular phase. However the compensation effect is not extended to the venous vessels (i.e. PVP and LVP) and the extracellular enhancement of the liver parenchyma. Instead, the lower amount of gadolinium is related to a significantly lower signal increase in these structures compared with

either a double dose of gadoxetate or a single dose of a general purpose extracellular Gd based contrast agent (Gd-DTPA). Zech et al. demonstrated that enhancement in the PVP and LVP was not influenced significantly by the injection rate, but did improve with a double dose of gadoxetate. This latter approach would mean a double dose of gadolinium, which is not without drawbacks.

[0005] In an approach proposed by Bayer (clinical trial NCT02156739) patients received 0.1mmol/kg of the general purpose agent gadopentetate dimeglumine 20 minutes post-administration of 0.025mmol/kg gadoxetate. The additional injection of an extracellular agent 20 min post the administration of gadoxetate generates signal intensity of the liver vasculature to a level comparable to the gadoxetate enhanced liver, thereby rendering the liver plain white (with bright healthy hepatocytes and bright vessels). This approach aims to generate a uniform enhanced organ to improve lesion characterisation but does nothing to improve the relatively poor dynamic vascular phase of gadoxetate.

[0006] There is a need for improved methods to overcome the issues relating to poor dynamic phase imaging of gadoxetate.

SUMMARY OF THE INVENTION

[0007] In a first aspect the present invention provides a pharmaceutical preparation comprising:

(i) a first active pharmaceutical ingredient (API) having hepatocellular uptake and biliary excretion; and,

(ii) a second API having renal excretion;

[0008] wherein each of said first API and said second API is a metal chelate comprising a cheland and a paramagnetic metal ion, and wherein the ratio of said first API to said second API is from 1:10 to 4:1.

[0009] The present invention also provides in a second aspect a dose of a pharmaceutical preparation to be administered to a subject wherein said pharmaceutical preparation is as defined herein and wherein said dose comprises between 0.01-0.04 mmol *per* kilogram of said subject of said first API and between 0.01-0.1 mmol *per* kilogram of said subject of said second API with the proviso that the combined dose of said first API and second API does not exceed 0.125 mmol *per* kilogram of said subject.

[0010] In a third aspect the present invention provides a method comprising:

(a) administering a dose of a pharmaceutical composition to a subject wherein said dose is as defined herein;

(b) carrying out magnetic resonance imaging (MRI) on said subject following said administering step wherein magnetic resonance (MR) signals are detected from the subject or parts of the subject into which the composition has distributed;

(c) generating MR images and/or MR spectra from the detected MR signals.

[0011] It is known that the dynamic vascular phase after bolus injection of an MRI contrast agent is of high importance for accurate visualization of normal vascular structures and the assessment of their relation to pathologic processes for diagnosis and treatment planning. The present invention demonstrates an improvement in sustained vascular enhancement across all vascular phases especially in the late PVP and LVP with a comparative delayed post-vascular phase to the liver specific agent. The additional vascular signal is useful in liver lesion characterisation and could facilitate vascular biomarker profiling such as wash in and wash out patterns of lesion enhancement in addition to the conventional lesion delayed enhancement profile.

[0012] The pharmaceutical preparations of the present invention have been demonstrated to provide a sustained vascular enhancement (which may act as a surrogate marker of detecting vascular lesion in different phases). The improved relative vascular intensity performance facilitates simultaneous assessment of both vascular and delayed enhancement of liver lesions with a similar or even reduced gadolinium burden to patients compared with known protocols.

BRIEF DESCRIPTION OF THE FIGURES

[0013] Figure 1 illustrates examples of the images obtained in a MRI procedure using a first API (bottom) and a second API (top) of the present invention.

[0014] Figure 2 shows the relaxivity values of a number of commercially-available MRI agents.

[0015] Figure 3 illustrates the peak signal intensity curves for the aorta, inferior vena cava (IVC), portal vein (PV) and liver parenchyma (A to E) and peak arterial enhancement for each test item (F) described in the Examples below.

[0016] Figure 4 illustrates the relative vascular intensity (RVI) curves for the aorta, inferior vena cava (IVC) and portal vein (PV) (A to E) and total AUC RVI for each test item (F) obtained as described in the Examples below.

[0017] Figure 5 shows the percentage relative vascular intensity (1- RVI%) for the arterial phase (AP) at 30 sec, the portal venous phase (PVP) at the late venous phase (LPV) 60 sec and late (PV) at 120 sec for each test item evaluated in the Examples described below.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0018] To more clearly and concisely describe and point out the subject matter of the claimed invention, definitions are provided hereinbelow for specific terms used throughout the present specification and claims. Any exemplification of specific terms herein should be considered as a non-limiting example.

[0019] The terms "comprising" or "comprises" have their conventional meaning throughout this application and imply that the agent or composition must have the essential features or components listed, but that others may be present in addition. The term 'comprising' includes as a preferred subset "consisting essentially of" which means that the composition has the components listed without other features or components being present.

[0020] In a first embodiment the present invention provides a pharmaceutical preparation. The term "pharmaceutical preparation" is taken to mean any pharmaceutically-acceptable preparation comprising the first API and the second API as defined herein that permits their simultaneous administration.

[0021] The term "active pharmaceutical ingredient" can be understood to mean is that ingredient in a pharmaceutical preparation that is biologically active. In the context of the present invention the term "biologically active" should be understood to mean for the purposes of *in vivo* imaging rather than as a therapeutic agent.

[0022] Following administration, both the first API and the second API of the present invention rapidly equilibrate in the intravascular and interstitial fluid compartments during what is typically referred to as the "dynamic vascular phase" (can also be referred to as the "extracellular phase"). The dynamic vascular phase can be understood to sequentially include the arterial

phase (AP), the portal venous phase (PVP) and the late venous phase (LVP). In the case of the first API of the present invention, it also demonstrates "hepatocellular uptake and biliary excretion", which is to say that following the dynamic vascular phase the API is taken up by hepatocytes and the cleared *via* the hepatobiliary system. In one embodiment, this hepatocellular uptake and biliary excretion represents a significant proportion of the clearance of said first API. In one embodiment the proportion of hepatobiliary clearance of said first API is >10%, in another embodiment >20%, in a further embodiment >30%, and in a yet further embodiment >40%. In one embodiment the proportion of hepatobiliary clearance of said first API is between 10-50%, in another embodiment between 20-50%, in a further embodiment between 30-50% and in a yet further embodiment between 40-50%. The first API has a relatively poor dynamic vascular phase compared with the second API and in particular does not demonstrate what is termed "sustained vascular enhancement", which is to say enhancement continuing into the PVP and LVP. In some embodiments the first API may have a complete or near complete absence of enhancement in the PVP and LVP, known as an "enhancement defect". The second API on the other hand does not have this level of hepatocellular uptake and biliary excretion but rather is primarily excreted *via* the kidneys following the dynamic vascular phase, i.e. it has a "renal excretion". In one embodiment this renal excretion of said second API can be regarded as a dedicated renal excretion, which is to say that the proportion of hepatobiliary clearance of said second API is negligible. In one embodiment the proportion of said second API cleared by hepatobiliary clearance is no more than 10%. In one embodiment the proportion of said second API cleared by hepatobiliary clearance is no more than 5%.

[0023] The term "metal chelate" in the context of the present invention is taken to mean a coordination complex wherein a paramagnetic metal ion is bonded to a surrounding array of molecules or anions comprised in a cheland. A "cheland" is defined herein as an organic compound capable of forming coordinate bonds with a paramagnetic metal ion through two or more donor atoms. In a typical cheland suitable for the present invention 2-6, and preferably 2-4, metal donor atoms are arranged such that 5- or 6-membered rings result (by having a non-coordinating backbone of either carbon atoms or non-coordinating heteroatoms linking the metal donor atoms). Examples of donor atom types which bind well to paramagnetic metal ions as part of chelating agents are: amines, thiols, amides, oximes, and phosphines. It is strongly preferred that the metal chelate of the present invention is "resistant to transchelation", i.e. does not readily

undergo ligand exchange with other potentially competing ligands for the metal coordination sites. Potentially competing ligands include the metal chelate itself plus other excipients in the preparation, or endogenous compounds *in vivo*.

[0024] A "paramagnetic metal ion" has unpaired electrons that behave as molecular magnetic dipole moments. The local magnetic field of a paramagnetic metal ion reduces the T1 and T2 relaxation times of surrounding hydrogen nuclei due to dipolar interactions between the paramagnetic ions and the hydrogens.

[0025] The "ratio of said first API to said second API" refers to the relative amounts of each of said first API to said second API present in said pharmaceutical preparation. In one embodiment the amount of each of said first API to said second API is defined as a molar amount.

[0026] Paramagnetic metal ions suitable for use in MRI are well-known to those of skill in the art as taught for example by Schouman-Claeys and Frija in the chapter "Contrast media" in "MRI of the Body" (2012 Springer Berlin Heidelberg; Daniel Vanel & Michael T. McNamara, Eds.). In one embodiment of the invention said paramagnetic metal ion is a transition metal or a lanthanide. In another embodiment of the invention said paramagnetic metal ion is selected from the group comprising Eu, Gd, Dy, Ho, Cr, Mn and Fe. In a further embodiment of the invention said paramagnetic metal ion is selected from the group comprising Gd, Mn, Fe and Cr. In a yet further embodiment of the invention said paramagnetic metal ion is selected from the group comprising Gd(III) and Mn(II). In a still further embodiment of the invention said paramagnetic metal ion is Gd(III).

[0027] For use in MRI, paramagnetic metal ions are administered as metal chelates in order to avoid any toxic effects of these metal ions in their free form. As well as the paramagnetic metal ion being stably complexed, the geometry of the cheland should be such that the paramagnetic effectiveness of the metal ion is maintained. In one embodiment the cheland is any ligand capable of producing a highly stable metal chelate complex, e.g. one with a thermodynamic stability constant of at least 10^{12}. In various embodiments the cheland can be a linear, cyclic or branched chelating agent, e.g. a linear mono- or polychelant, a macrocyclic chelant or a branched polychelant (e.g. a dendrimeric polychelant). In one embodiment the cheland will be a polyaminopolyoxyacid (e.g. polyaminopolycarboxylic acid). Examples are suitable chelands are described in the art, such as one of the mono and polychelants suggested for lanthanide chelation

taught in the patent publications of Nycomed (including Nycomed Imaging and Nycomed Salutar) , Sterling Winthrop, Schering, Bracco, Squibb, Mallinckrodt , Guerbet and Metasyn, e.g. US4647447, EP0071564-A, WO1996003154, WO1996001655, EP0430863-A, WO1996041830, WO1993010824, WO1989000557, EP0292689-A, EP0232751-A, EP0230893-A, EP0255471-A, EP0277088-A, EP0287465-A. US5334371 discloses macrocyclic polyaza bicyclo compounds containing Mn(II) ions. WO2011073371 (GE Healthcare AS) discloses chelands optimized for chelation of Mn(II) that are kinetically stable and show optimal water exchange kinetics. WO2011121002 and US20140086846 (General Electric Company) teach cheland structures optimized for chelation of transition metals and in particular iron. DTPA-bisalkylamides and methods for their preparation are disclosed in US-A-4687659 and DTPA-bis(hydroxyalkyl-amides) and methods for their preparation are disclosed in US-A-4826673 and EP-A-130934. WO2009103744, WO2016083597, WO2016083605 and WO2016083600 all describe methods to obtain gadolinium-based MRI contrast agents consisting of a DOTA cheland and gadolinium (Gd^{3+}).In one embodiment of the pharmaceutical preparation of the invention said cheland is selected from the group comprising: diethylenetriaminepentaacetic acid (DTPA); 4-carboxy-5, 8, 11-tris(carboxymethyl)-1-phenyl-2oxa-5, 8, 11-triazatridecan-13-oic acid (BOPTA); 1, 4, 7, 10-tetraazacyclododecan-1, 4, 7-triactetic acid (DO3A); 1, 4, 7, 10-tetraazacyclododecan-1, 4, 7, 10-tetraactetic acid (DOTA); ethylenediaminotetraacetic acid (EDTA); 10-(2-hydroxypropyl)-1, 4, 7, 10-tetraazacyclododecan-1, 4, 7-triacetic acid (HP-DO3A); 2-methyl-1, 4, 7, 10-tetraazacyclododecan-1, 4, 7, 10-tetraacetic acid (MCTA); tetramethyl-1, 4, 7, 10-tetraazacyclododecan-1, 4, 7, 10-tetraacetic acid (DOTMA); 3, 6, 9, 15-tetraazabicyclo[9.3.1]pentadeca-1(15),11, 13-triene-3, 6, 9-triacetic acid (PCTA); N, N'Bis(2-aminoethyl)-1,2-ethanediamine (TETA); 1,4,7,10-tetraazacyclotridecane- N,N',N",N'"-tetraacetic acid (TRITA); 1,12-dicarbonyl, 15-(4-isothiocyanatobenzyl) 1, 4, 7, 10, 13-pentaazacyclohexadecane-N, N', N" triaceticacid (HETA); [(2S,5S,8S,11S)-4,7-bis-carboxymethyl-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclo-dodecan-1-yl]acetic acid, (M4DO3A); 1-O-Phosphonomethyl- 1,4,7, 1-O-tetraazacyclododecane- 1,4,7-triacetic acid (MPDO3A); hydroxybenzyl-ethylenediamine-diacetic acid (HBED); N,N'-ethylenebis-[2-(o-hydroxyphenolic)glycine](EHPG); 10–[(1SR,2RS)–2,3–dihydroxy–1–hydroxymethylpropyl]–1,4,7,10– tetraazacyclododecane–1,4,7–triacetic acid (BT-DO3A); and, 2-[bis[2-[carboxylatomethyl-[2-(2-methoxyethylamino)-2-oxoethyl]amino]ethyl]amino]acetate (DTPA-

BMEA).

[0028] A "derivative" of a cheland is to be understood in the context of the present invention as the cheland comprising a further chemical group that does not interfere with the chelating properties of the cheland. Such a chemical group may be included in order to functionalise the metal chelate with a biological targeting moiety or to adjust the pharmacokinetic properties of the metal chelate. Non-limiting examples of cheland derivatives include: DTPA derivatives such as N-[2-[bis(carboxymethyl)amino]-3-(4-ethoxyphenyl)propyl]-N-[2-[bis(carboxymethyl)-amino]ethyl]-L-glycine (EOB-DTPA), N,N-bis[2-[bis(carboxymethyl)amino]-ethyl]-L-glutamic acid (DTPA-Glu), N,N-bis[2-[bis(carboxymethyl)amino]-ethyl]-L-lysine (DTPA-Lys), N,N-bis[2-[carboxymethyl[(methylcarbamoyl)methyl]amino]-ethyl] glycine (DTPA-BMA); DOTA derivatives such as 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid mono-(N-hydroxysuccinimidyl) ester (DOTA-NHS) and [(2S,5S, 8S, 11S)-4,7,10-tris-carboxymethyl-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecan-1-yl]acetic acid (M4DOTA); DOTMA derivatives such as (R)-2-[(2S,5S,8S,11S)-4,7,10-tris-((R)-1-carboxyethyl)-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecan-1-yl]propionic acid (M4DOTMA); PCTA derivatives such as PCTA12 and cyclo-PCTA12; and TETA derivatives such as N, N'-Bis(2-aminoethyl)-1,2-ethanediamine-N- hydroxy-succinimide ester (TETA-NHS).

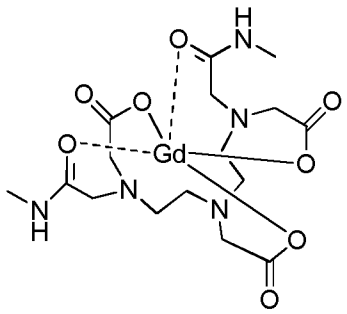
[0029] In a further embodiment of the pharmaceutical preparation of the invention said cheland is selected from DTPA, DOTA or derivatives thereof. In a yet further embodiment of the pharmaceutical preparation of the invention said cheland or derivative thereof is selected from EOB-DTPA, DTPA-BMA, DTPA-BMEA, DTPA, DOTA, BOPTA, HP-DO3A and BT-DO3A.

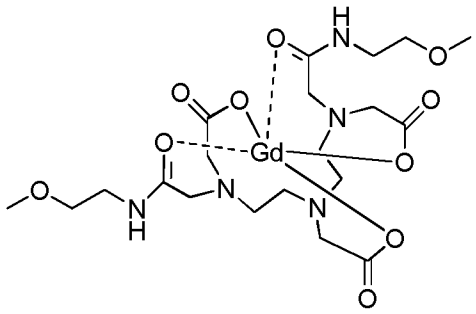
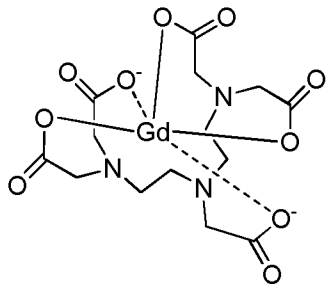
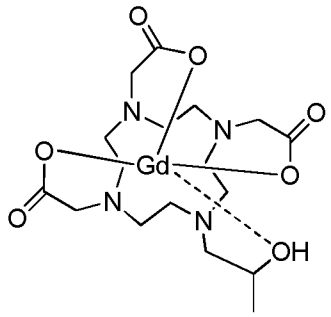
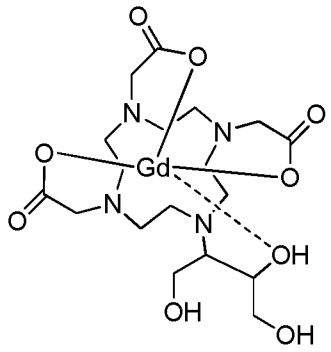
[0030] Each of the first API and second API may be prepared by methods well known to those of skill in the art by reacting a suitable cheland and a suitable paramagnetic metal together. The reaction is typically performed in an aqueous solution, e.g. in distilled water optionally containing a miscible co-solvent, at an elevated temperature, e.g. 70 to 95°C, preferably 80-90°C. During the reaction the pH is generally 3 to 6 and may be controlled by addition of an acid or base, for example an acid or base which produces pharmaceutically acceptable neutralisation products, such as hydrochloric acid and sodium hydroxide . The progress of the reaction will generally be monitored to determine the residual quantities of unreacted cheland or paramagnetic metal ion, with extra portions optionally being added until the reaction is deemed

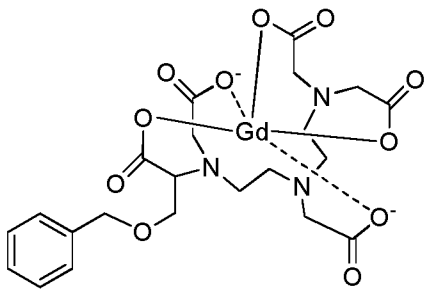
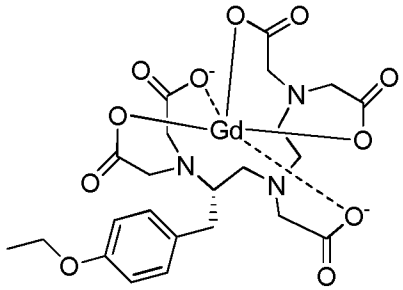
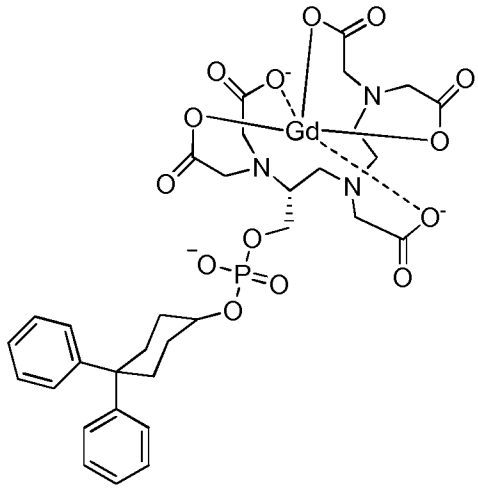
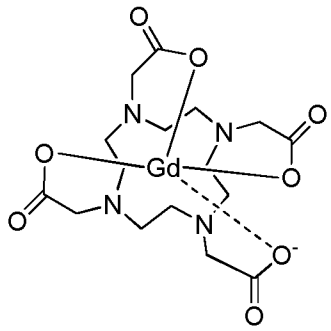
to be complete, e.g. when a stable low concentration of cheland and negligible free paramagnetic metal ion is detected. Typically thereafter the reaction mixture is cooled, e.g. to below 25°C. If necessary the pH of the reaction mixture is then adjusted, e.g. to about 6, for example using sodium hydroxide. The solution is then filtered and the metal chelate is isolated using methods well-known to the skilled person, e.g. by crystallisation chromatography, and the like and thereafter admixed with a biocompatible carrier and one or more excipients as defined herein. In one embodiment of the pharmaceutical preparation of the invention the ratio of said first API to said second API is from 1:5 to 3:2. In another embodiment said ratio is from 1:4 to 1:1. In a further embodiment said ratio is 1:1. In a yet further embodiment said ratio is 1:2. In a still further embodiment said ratio is 1:3. In a still further embodiment said ratio is 1:4.

[0031] The combined API dose of the present invention should not exceed the recommendations for a single API dose. In certain embodiments the total cumulative dose is less than or equal to 0.125 mmol/kg.

[0032] The chemical structures are provided in the table below of certain known APIs and the commercially-available MRI pharmaceutical preparations in which they are formulated (note that counter ions, if present, are omitted from the chemical structures) :

Product Name (Chemical Name)	**Chemical Structure**
Omniscan (gadodiamide)	

Optimark (gadoversetamide)	
Magnevist (gadopentate dimeglumine)	
ProHance (gadoteridol)	
Gadavist (gadobutrol)	

MultiHance (gadobenate dimeglumine)	
Eovist (gadoxetate disodium)	
Ablavar (gadofosveset trisodium)	
Dotarem (gadoterate meglumine)	

[0033] In one embodiment of the pharmaceutical preparation of the invention said first API is

gadoexetate.

[0034] In one embodiment of the pharmaceutical preparation of the invention said second API is selected from the group comprising gadodiamide, gadoversetamide, gadopentate, gadoteridol, gadobutrol, gadobenate, gadofosveset and gadoterate. In another embodiment, said second API is selected from the list comprising gadoteridol, gadobutrol and gadoterate. In a further embodiment, said second API is selected from gadobutrol and gadoterate.

[0035] Gadoxetate has up to 50% hepatobiliary excretion in the normal liver. After intravenous injection, gadoxetate distributes into the vascular and extravascular spaces during the dynamic vascular phase and progressively into the hepatocytes and bile ducts during the hepatobiliary phase. Gadoxetate adds substantial information during the hepatobiliary phase, improving the detection and characterization of focal liver lesions and diffuse liver disease (Beers 2012 J Hepatol; 57(2): 421–429).

[0036] Figure 1 shows MR images of a human liver obtained over time using non-limiting examples of a first API (bottom= gadoxetate) and a second API (top= gadoterate).

[0037] The "pre" image (sometimes referred to as "pre-contrast image") is acquired prior to arrival of any API in the image. The "dynamic" image (sometimes referred to as "dynamic contrast-enhanced MRI") is acquired immediately after the arrival of any API in the image. The "delayed" image (sometimes referred to as "delayed contrast-enhanced MRI") is acquired at a time point after the arrival of any API in the image. For the three distinct phases of the dynamic vascularphase: in AP, the API has been delivered mainly through the hepatic artery; in PVP, the API in the liver has been delivered also through the inferior vena cava and portal vein; and in the LVP the second API is distributed mainly extracellularly. The "HBP" (hepatobiliary phase) image is acquired at a time point when the first API has had sufficient time to accumulate in the hepatocytes to allow acquisition with good contrast-to-noise.

[0038] In one embodiment of the pharmaceutical preparation of the invention said first API and said second API are provided separately but configured to permit simultaneous administration. For example, it is envisaged that the two APIs may be provided in separate syringes that are placed in an apparatus (injector) capable of injecting the two syringes at the same time, with individual rate and dosing control. The two APIs are therefore mixed upon leaving the individual syringes, before entering the patient. In an alternative embodiment, the two APIs may be placed

in a double barrel syringe so as to be separated until the point of injection. In a further embodiment, the two APIs may be provided in one syringe, separated by a membrane that is pierced upon injection allowing for mixing upon injection.

[0039] In one embodiment of the pharmaceutical preparation of the invention each of said first API and said second API are provided as a pharmaceutical composition together with a biocompatible carrier.

[0040] The "biocompatible carrier" is a fluid, especially a liquid, in which the first API or the second API is (or both APIs together are) suspended or dissolved, such that the resulting composition is physiologically tolerable, i.e. can be administered to the mammalian body without toxicity or undue discomfort (which can be understood to be a definition of the term "suitable for mammalian administration").

[0041] In an alternative embodiment the pharmaceutical preparation of the invention is provided as a pharmaceutical composition wherein said first API and said second API are formulated together with a biocompatible carrier. For this embodiment, the two APIs may be premixed and distributed as a new formulation containing optimal proportions of the first API and the second API as defined herein.

[0042] In one embodiment the pharmaceutical composition of the invention may comprise one or more pharmaceutically acceptable excipients. Non-limiting examples of suitable pharmaceutically acceptable excipients include buffering agents, stabilizers, antioxidants, osmolality adjusting agents, buffers, pH adjusting agents, excess cheland, weak complexes of physiologically tolerable ions such as calcium chelates, calcium or sodium salts like calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate. These and other suitable excipients will be well known to those of skill in the art and are further described in e.g. WO1990003804, EP0463644-A, EP0258616-A and US5876695 the content of which are incorporated herein by reference. The pharmaceutical composition of the invention in one embodiment is in a form suitable for parenteral administration, for example injection. Thus the APIs of the present invention may be in conventional pharmaceutical administration forms such as solutions, suspensions and dispersions in physiologically acceptable carrier media, for example water for injections. The pharmaceutical composition according to the invention may therefore be formulated for administration using physiologically acceptable excipients in a

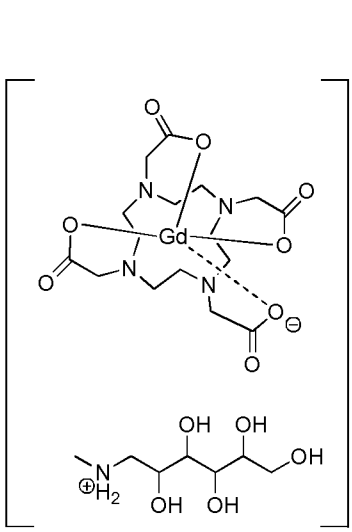
manner fully within the skill of the art. For example, the APIs, optionally with the addition of pharmaceutically acceptable excipients, may be suspended or dissolved either separately or together in an aqueous medium, with the resulting solution or suspension then being sterilized. Non-limiting examples of pharmaceutically acceptable excipients include, for example, physiologically biocompatible buffers (as for example, tromethamine hydrochloride), slight additions of other chelands (as for example, diethylenetriaminepentaacetic acid) or, optionally, calcium or sodium salts (for example, calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate). For MRI procedures the typical mode of administration is parenteral, e.g. intravenous, administration. Parenterally administrable forms, e.g. intravenous solutions, should be sterile and free from physiologically unacceptable agents and should have low osmolality to minimize irritation or other adverse effects upon administration and thus the pharmaceutical composition should be isotonic or slightly hypertonic. Suitable vehicles include aqueous vehicles customarily used for administering parenteral solutions such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection and other solutions such as are described in Remington's Pharmaceutical Sciences, 22nd Edition (2006 Lippincott Williams & Wilkins) and The National Formulary (https://books.google.com/books?id=O3qixPEMwssC&q=THE+NATIONAL+FORMULARY&dq=THE+NATIONAL+FORMULARY&hl=en&sa=X&ved=0CC8Q6AEwAGoVChMImfPHrdTqyAIVJfNyCh1RJw_E). The pharmaceutical compositions can also contain preservatives, antimicrobial agents, buffers and antioxidants conventionally used in parenteral solutions, and other excipients compatible with the chelands and related metal chelates and which will not interfere with the manufacture, storage or use of the final products.

[0043] In one embodiment each of the first API and the second API comprises a charge-balancing counterion, which may be an organic cation or an inorganic cation. Thus, in one embodiment, the charge balancing counterion is an inorganic cation. Non-limiting examples of inorganic cations include alkali metal cations, alkaline earth metal cations, transition metal cations, and inorganic ammonium cations (NH_4^+). In another embodiment, the charge balancing counterion is an organic cation, for example an organic ammonium cation, an organic phosphonium cation, an organic sulfonium cation, or a mixture thereof. In one embodiment, the charge balancing counterion is the ammonium salt of an aminosugar such as the 2-(N,N,N-trimethylammonium)-2-deoxyglucose. In one embodiment, the charge balancing counterion is

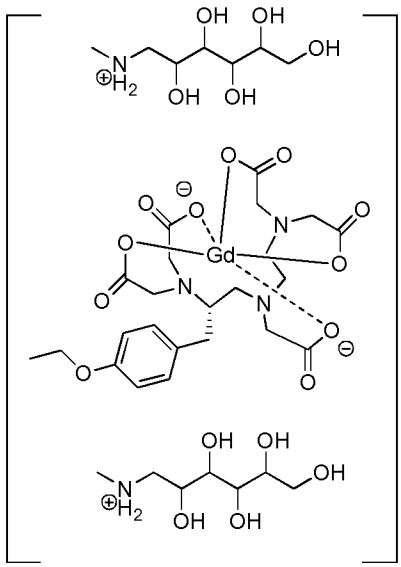
the protonated form of N-methyl glucamine.

[0044] Methods for the preparation of a pharmaceutical composition are well known in the art. For preparation of a pharmaceutical composition comprising the first API and the second API together with a biocompatible carrier, the metal chelates may be prepared separately and then admixed in the desired ratio. For the pharmaceutical composition to be administered parenterally, i.e. by injection its preparation further comprises steps including removal of organic solvent, addition of a biocompatible buffer and any optional further ingredients such as excipients or buffers. For parenteral administration, steps to ensure that the pharmaceutical composition is sterile and apyrogenic also need to be taken.

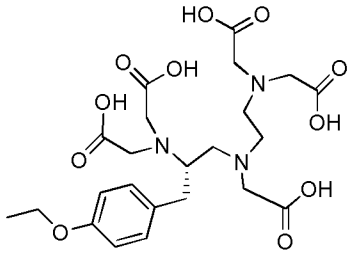
[0045] In one embodiment where the first API and the second API are present in the same pharmaceutical composition it is specifically formulated to reduce the risk of precipitation and transmetallation. In one embodiment the choice of buffer can act to eliminate the risk of precipitation of salt forms of the APIs. In one embodiment, the addition of excess cheland can act to stabilise the composition to avoid transmetallation. In one embodiment of the pharmaceutical preparation of the invention gadoexetate and gadoterate meglumine are formulated together with an excess of the free acid of EOB-DTPA, and wherein meglumine is a sole buffering agent. The relative composition of gadoexetate and gadoterate meglumine can be determined from imaging efficacy. In another embodiment this pharmaceutical preparation with gadoexetate and gadoterate meglumine comprises megluminium instead of calcium and sodium ions, which eliminates the risk of precipitation of the sodium salt of gadoterate. This embodiment is further advantageous in that the formulation is simplified since the buffering agent commonly used in gadoexetate formulations, trometamol, is not included. The chemical composition of this embodiment is illustrated below:



GdDOTA-Meglumine

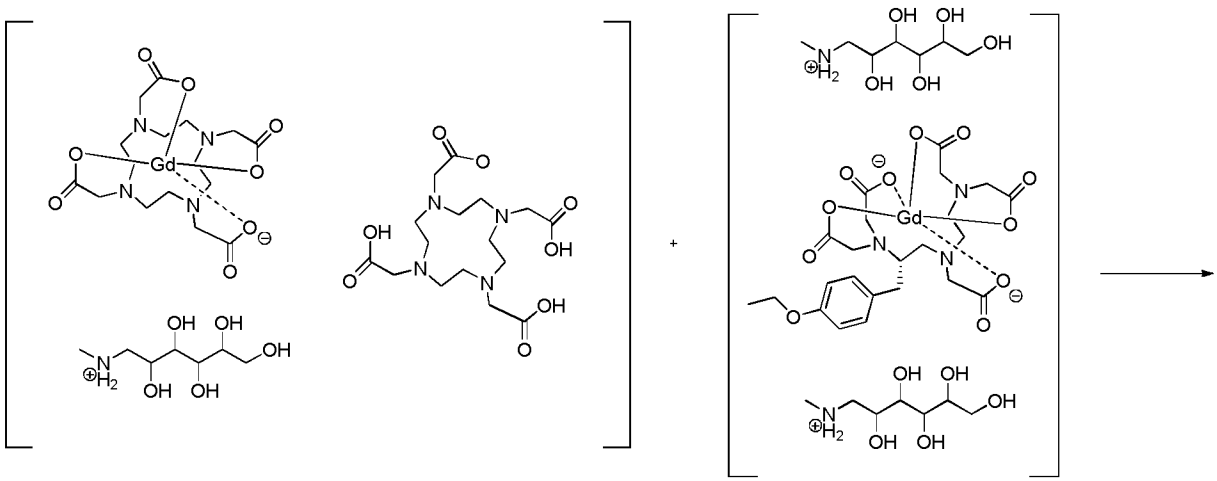


GdEOB-DTPA-bis-Meglumine

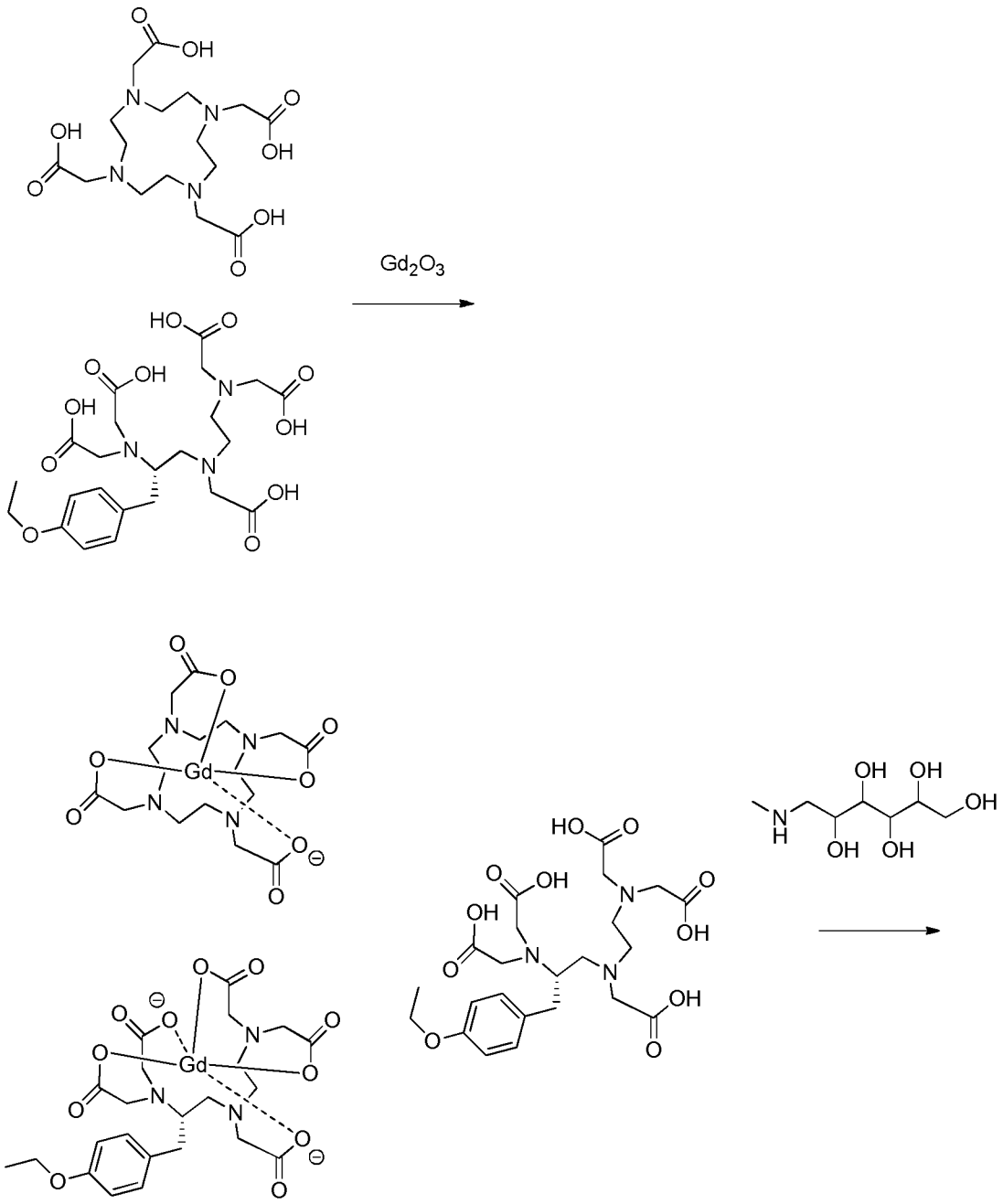


EOB-DTPA

[0046] The above formulation could be obtained by mixing commercially available liquid bulk of gadoterate meglumine with Gd-EOB-DTPA-bis-megluminium salt/solution as shown in the scheme below.



[0047] In another embodiment a process can be used that utilizes commercially available DOTA and cheland EOB-DTPA in an *in situ* complexation reaction, where gadolinium oxide is added to DOTA/EOB-DTPA ligand mixture and the proportion of excess free ligand (EOB-DTPA) is set by a measure and adjust step (as described e.g. in EP2242515-B1) prior to pH adjustment with meglumine.



[0048] It is known that there is a correlation between the amount of excess cheland in a Gd chelate formulation and the amount of Gd deposited in animal models (Sieber 2008 J Mag Res Imaging; 27(5): 955-62). Therefore, in another embodiment where the first API and the second API are formulated together and at least one of said first API and said second API comprise Gd, an amount of excess cheland is selected that can act as a Gd scavenger so as to reduce or prevent release of Gd from the formulation post injection. The optimal amount of free cheland will

result in a pharmaceutical composition having suitable physicochemical properties (i.e. viscosity, solubility and osmolality) and avoiding toxological effects such as zinc depletion in the case of too much free cheland.

[0049] In a second embodiment the pharmaceutical preparation of the present invention is provided as a dose to be administered to a subject.

[0050] In the present invention the term "dose" is taken to mean a measured quantity of the pharmaceutical preparation as defined herein to be administered to a subject at one time for the purposes of an MRI procedure.

[0051] The "subject" can be any human or animal subject. In one embodiment the subject is a mammal, i.e. an intact mammalian body *in vivo*. In one embodiment the subject is a living human or non-human animal body.

[0052] In one embodiment of the dose of the invention the combined dose of said first API and second API is less than 0.125 mmol per kilogram of said subject.

[0053] In one embodiment the dose of the invention comprises between 0.02-0.03 mmol *per* kilogram of said subject of said first API.

[0054] In the dose of the present invention the ratios can be modified as the dynamic contribution from the first API can be harnessed during the dynamic phase of the second API. In certain embodiments this allows for a reduction of contrast agent dose, while maintaining sufficient enhanced arterial phase (in combination with the signal contribution from the first API).

[0055] In certain embodiments of the present invention the absolute quantities and relative amounts of each of said first API and said second API are determined based on the relaxivity of said second API. The concept of "relaxivity" of an MRI agent is well known to those of skill in the art and refers to the ability of magnetic compounds to increase the relaxation rates of the surrounding water proton spins. Relaxivity is used to improve the contrast of an MR image, and to study tissue specific areas where the contrast agent better diffuses or to perform functional MRI. The relaxivity of MRI agents depends on the molecular structure and kinetic of the complex. Relaxivity depends on the temperature, field strength, and substance in which the contrast agent is dissolved. In the context of the present invention the conditions for which the

relaxivity values have been set are *in vivo* at 37°C (as opposed to e.g. in water at ambient temperatures of ~20°C). The relaxivities of 8 commonly-used Gd-based MRI agents have been described by Shen *et al* (2015 Invest Radiol; 50(5): 330-8). Figure 2 illustrates the relaxivity values in blood of a number of known MRI agents at 1.5T and 3T.

[0056] In one embodiment the dose of the invention comprises between 0.025-0.1 mmol *per* kilogram of said subject of said second API wherein said second API has a relaxivity ≥ 3 mM-1s-1 at field strengths of 1.5-3. The value ≥ 3 mM-1s-1 can in one embodiment be regarded as encompassing 3-5 mM-1s-1, in another embodiment 3-4 mM-1s-1, in a further embodiment 4-5 mM-1s-1 and in a yet further embodiment 3.5 mM-1s-1. In certain embodiments a dose in accordance with the embodiments of this paragraph is selected from:

0.02 mmol *per* kilogram of said subject of said first API and between 0.04-0.1 mmol *per* kilogram of said subject of said second API; or,

0.02 mmol *per* kilogram of said subject of said first API and between 0.05-0.1 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.03-0.1 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.04-0.1 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and 0.1 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and 0.05 mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.025-0.1 mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.04-0.095 mmol *per* kilogram of said subject of said second API.

[0057] In one embodiment the dose of the invention comprises between 0.02-0.09 mmol *per* kilogram of said subject of said second API wherein said second API has a relaxivity ≥ 5 mM-

1s-1 at field strengths of 1.5-3 T. The value ≥ 5 mM-1s-1 can in one embodiment be regarded as encompassing 5-7 mM-1s-1 and in another embodiment 5-6 mM-1s-1. In certain embodiments a dose in accordance with the embodiments of this paragraph is selected from:

0.02 mmol *per* kilogram of said subject of said first API and between 0.03-0.09 mmol *per* kilogram of said subject of said second API; or,

0.02 mmol *per* kilogram of said subject of said first API and between 0.04-0.09 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.025-0.09 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.03-0.08 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and 0.05 mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.02-0.09 mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.03-0.075 mmol *per* kilogram of said subject of said second API.

[0058] In one embodiment the dose of the invention comprises between 0.02-0.07 mmol *per* kilogram of said subject of said second API wherein said second API has a relaxivity ≥ 7 mM-1s-1 and field strengths of 1.5-3 T. The value ≥ 7 mM-1s-1 can in one embodiment be regarded as encompassing ≥ 8 mM-1s-1 and in another embodiment 8-9 mM-1s-1. In certain embodiments a dose in accordance with the embodiments of this paragraph is selected from:

0.02 mmol *per* kilogram of said subject of said first API and between 0.02-0.07 mmol *per* kilogram of said subject of said second API; or,

0.02 mmol *per* kilogram of said subject of said first API and between 0.03-0.06 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.02-0.07 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.025-0.06 mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.02-0.06 mmol *per* kilogram of said subject of said second API.

[0059] In one embodiment the dose of the invention comprises between 0.01-0.06 mmol *per* kilogram of said subject of said second API wherein said second API has a relaxivity ≥ 9 mM-1s-1 at field strengths of 1.5-3 T. The value ≥ 9 mM-1s-1 can in one embodiment be regarded as encompassing 9-11 mM-1s-1 and in another embodiment 10 mM-1s-1. In certain embodiments a dose in accordance with the embodiments of this paragraph is selected from:

0.02 mmol *per* kilogram of said subject of said first API and between 0.02-0.06 mmol *per* kilogram of said subject of said second API; or,

0.02 mmol *per* kilogram of said subject of said first API and between 0.02-0.05 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.02-0.06 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.02-0.05 mmol *per* kilogram of said subject of said second API; or, 0.03 mmol *per* kilogram of said subject of said first API and between 0.01-0.05 mmol *per* kilogram of said subject of said second API.

[0060] In a third embodiment the present invention provides an MRI method comprising administration of a dose of the pharmaceutical preparation of the invention as defined herein.

[0061] Methods of administering and subjects envisaged as suitable have been described hereinabove in connection with the pharmaceutical composition. The pharmaceutical composition is administered in an amount suitable to enhance the contrast in the method of MR imaging. MRI methods using APIs such as the first API and the second API as described herein are well-known to those of skill in the art, e.g. as taught in Chapter 27 "Contrast Agents and Magnetic Resonance Imaging" in "Magnetic Resonance Imaging: Physical and Biological Principles" (4th Edition 2015 Elsevier, Stewart Carlyle Bushong & Geoffrey Clarke, Eds.) or in "Contrast Agents I: Magnetic Resonance Imaging" (2002 Springer-Verlang, Werner Krause, Ed.).

[0062] The method of the invention has utility as a method for diagnosis. The examples herein demonstrate that the method of the invention provides certain advantages that will be useful in the detection and characterization of focal liver lesions and diffuse liver disease compared with known such methods. The present inventors compared the performance of formulations comprising either gadoxetate (an example of a "first API" as defined herein) or gadoterate (an example of a "second API" as defined herein) as the sole API with that of a number of formulations comprising a combination of gadoxetate with either gadoterate or gadobutrol (another example of a "second API" as defined herein). The combination formulations represent embodiments of the pharmaceutical preparation according to the present invention and are referred to the Examples as "Combo" formulations. In the analysis of vascular intensity of the Combo formulations following administration of a dose *in vivo*, all formulations provided peak %RVI (%relative vascular intensity) at AP with decreased signal at the later PVP and LVP. A significant reduction of %RVI was found at PVP phase with the formulation having gadoxetate as the sole API compared to all other formulations tested (Combo 1, Combo 2, Combo 3 and gadoterate). This trend continued to decrease into LVP, with no vascular enhancement evident from gadoxetate at 120 secs post injection, demonstrating the poor dynamic vascular endurance of this liver specific agent. This enhancement defect in the post-vascular phase has been previously recognised as a pitfall of hepatobiliary agents compared to non-specific gadolinium based contrast (Frydrychowicz et al 2012, JMRI;35(3): 492–511). The AUC was significantly increased in all combo test items (Combo 1, Combo 2 and Combo 3) in comparison to gadoxetate (93.8 AU, 76.7 AU, 84.9 AU vs. 34.2 AU) and gadoterate (93.8 AU, 76.7 AU, 84.9 AU vs. 63.2 AU). These results demonstrate that the pharmaceutical preparation of the present invention provides both good early arterial enhancement as well as an improvement in sustained RVI throughout the entire vascular phase. These observations were made for the Combo formulations not only in contrast to a formulation including gadoxetate as the sole API but also in contrast to a formulation including gadoterate as the sole API.

[0063] This written description uses examples to disclose the invention, including the best mode, and also to enable any person skilled in the art to practice the invention, including making and using any devices or systems and performing any incorporated methods. The patentable scope of the invention is defined by the claims, and may include other examples that occur to those skilled in the art. Such other examples are intended to be within the scope of the claims if they have

structural elements that do not differ from the literal language of the claims, or if they include equivalent structural elements with insubstantial differences from the literal languages of the claims. The entire disclosures of all documents mentioned herein are incorporated herein by reference.

EXAMPLES

[0064] List of Abbreviations used in the Examples

AUC	area under the curve
ICP-MS	inductively-coupled plasma mass spectrometry
IV	intravenous
FoV	field of view
IVC	inferior vena cava
LAVA	Liver Acquisition with Volume Acquisition
MRI	magnetic resonance imaging
NEX	number of excitations
NMR	nuclear magnetic resonance
PAC	Port-a-cath
PV	intrahepatic portal vein
ROI	region of interest
RVI	relative vascular intensity
SI	signal intensity
TE	echo time
TR	repetition time
UZB	Universitair Ziekenhuis Brussel

[0065] Test Items

[0066] The following test items were used to evaluate the present invention:

(i) **Gadoxetate** (disodium;2-[[2-[bis(carboxylatomethyl)amino]-3-(4-ethoxyphenyl)propyl]-[2-bis(carboxylatomethyl)amino]ethyl]amino]acetate, gadolinium(3+)) was purchased from Bayer Pharma AG (D-13342 Berlin Germany). The commercially supplied gadoxetate formulation contains 181.43 mg/ml gadoxetate disodium, equivalent to 0.25 mmol/ml, the

excipients caloxetate trisodium, trometamol, hydrochloric acid and/or sodium hydroxide (for pH adjustment), and water for injection. For use in these studies, it was diluted in water for injection (BBraun) to a concentration of 0.083 mmol/ml and administered at 0.3 ml/kg to give the final dose (0.025 mmol/kg).

(ii) **Gadoterate** (2-[4, 7 -his(carboxylatomethyl)-1 0-(carboxymethyl)-1 ,4, 7,10-tetrazacyclododec-1-yl]acetate; gadolinium(3+)) was manufactured by GE Healthcare. Gadoterate meglumine contains 279.3 mg/ml gadoterate, equivalent to 0.5 mmol/ml and the excipients meglumine and water for injection. For use in these studies, it was diluted in water for injection (BBraun) to a concentration of 0.333 mmol/ml and administered at 0.3 ml/kg to give the final dose (0.1 mmol/kg).

(iii) **Combo 1** is a combination of gadoxetate and gadoterate. Combo 1 was formulated in water for injection (BBraun) to a concentration of 0.083 mmol/ml and 0.333 mmol/ml respectively. Administration of 0.3 ml/kg was given for a final dose of gadoxetate (0.025 mmol/kg) and gadoterate (0.1 mmol/kg).

(iv) **Combo 2** is a combination of gadoxetate and gadoterate. Combo 2 was formulated in water for injection (BBraun) to a concentration of 0.083 mmol/ml and 0.167 mmol/ml respectively. Administration of 0.3 ml/kg was given for a final dose gadoxetate (0.025 mmol/kg) and gadoterate (0.05 mmol/kg).

(v) **Combo 3** is a combination of gadoxetate and gadobutrol. Gadobutrol (1 0-(2,3-Dihydroxy-1-hydroxymethylpropyl)-1 ,4, 7,10- tetraazacyclododecane-1 ,4, 7 -triacetic acid) was purchased from Bayer Pharma AG (D-13342 Berlin Germany). Gadobutrol commercially supplied formulation contains 604.72 mg/ml gadobutrol, (equivalent to 1.0 mmol/ml) and water for injection. For use in these studies, it was diluted in water for injection (BBraun) to a concentration of 0.333 mmol/ml (equal molar concentration to gadoterate). The diluted gadobutrol solution was used for the preparation of Combo 3.

Combo 3 was formulated in water for injection (BBraun) to a concentration of 0.083 mmol/ml for gadoxetate and 0.167 mmol/ml for gadobutrol. Administration of 0.3 ml/kg was given for a final dose of gadoxetate (0.025 mmol/kg) and gadobutrol (0.05 mmol/kg).

[0067] Table 1 below summarises the test items and dose that was administered *in vivo*. All test items were prepared with saline to a standard 15ml solution.

Material/ Test Item	**Gadoxetate dose (mmol/kg)**	**Gadoterate dose (mmol/kg)**	**Gadobutrol dose[#] (mmol/kg)**
Gadoxetate	0.025	-	-
Gadoterate	-	0.1	-
Combo 1	0.025	0.1	-
Combo 2	0.025	0.05	-
Combo 3	0.025	-	0.05

[#]Gadobutrol formulation was diluted to 0.333mmol/ml (equal molar concentration to gadoterate)

[0068] Dosing regimen rationale

[0069] The dose range of test items administered for the individual and the Combo 1 dose regimens have been selected to reflect typical clinical doses for these agents. Combo 2 and Combo 3 have a reduced cumulative gadolinium dose by lowering the dose of either gadoterate or gadobutrol (50% below the standard clinical dose = 0.05 mmol/kg) whilst maintaining the dose of the gadoxetate.

[0070] *In vitro* relaxivity measurements were used to evaluate the efficacy (relaxivity) of the Combo formulations compared to the standalone commercial contrast agents. Longitudinal relaxation times were measured in 150 mM saline solution at 37°C using a Minispec Mq benchtop NMR relaxometer (Bruker Instruments, Rheinstetten, Germany) operating at 60 MHz. The longitudinal relaxivity of the complexes were calculated by plotting the reciprocal of the T1 relaxation time versus the gadolinium concentration as determined via ICP-MS for each

individual agent and the Combo formulations tested.

[0071] Experimental design

[0072] The study was approved by the Universitair Ziekenhuis Brussel (UZB), Belgium local ethics committee for animal experiments on the 9th March 2016 (EC number: 16-272-4). All animal experiments were carried out in accordance with the applicable laws and regulations. Naïve minipigs (Gottingen minipigs, Ellegaard Gottingen Minipigs, Denmark) were chosen as the model as its cardiac function and vascular dynamics closely resembles that of the human allowing optimal spatial and temporal resolution for the evaluation of the dynamic vascular phase.

[0073] The study consisted of five dosing groups (2 groups of contrast agent administered as single stand-alone dose; 3 groups administered with the Combo formulations). Each animal was tested once within each dosing group with a washout period of one week.

[0074] Procedures

[0075] For each MRI examination, anaesthesia was induced with a bolus of the Zoletil mixture (0.06 ml/kg, intramuscular) and maintained by an infusion of Nesdonal (0.6 ml/kg/h, intravenously (IV) administered). Test items were administered IV as a single injection via PAC unit (Port-a-cath, Power PAC II, 1.9 mm, Smiths Medical, Belgium). The test items were administered at a volume of 0.3 ml/kg using a power injector (Medrad Spectris Solaris) at a rate of 2 ml/s. Immediately following administration, 20 ml saline was passed through the tubing to flush any remaining test item.

[0076] Contrast-enhanced MR imaging

[0077] All MRI acquisitions were performed on a clinical 3.0T GE MR750w scanner (GE Discovery, GE Healthcare, Waukesha, WI) using an abdominal phase-array surface coil positioned on the abdomen of the pigs. A multiphase dynamic 3D T1w LAVA (Liver Acquisition with Volume Acquisition) was performed using bolus timing to capture the early arterial to the late venous vascular phase using the following imaging parameters: TR/TE = 2.9/1.3ms, FA = 12°, FoV = 42 x 40cm, matrix 220 x160, slice thickness = 3 mm, number of slices = 40, NEX = 1. The protocol also included a free-breathing navigated LAVA acquired at

both pre and post administration of test item (during the delayed enhancement phase).

[0078] Image analysis

[0079] Quantitative analysis on the time-resolved dynamic series was completed using the Advantage Windows VolumeShare 7 Workstation (GE Healthcare). Regions of interest (ROI) were placed on the aorta, the inferior vena cava (IVC), intrahepatic portal vein (PV) and normal liver parenchyma. Visual verification of all ROI locations was performed by an abdominal radiologist. For each test item, absolute signal intensity (SI) curves were analysed for each of the ROIs and expressed as peak value with inter-quartile ranges of 25% and 75%.

[0080] To calculate the vascular enhancement, relative vascular intensity (RVI) was normalised to liver parenchyma for the aorta, IVC and PV using the equation below.

[0081] Relative Vascular Intensity (RVI)=(SI (vessel)-SI(liver))/(SI (liver))

[0082] Using the RVI curves, composite vascular intensity curves were derived encompassing all vascular signal from the aorta, IVC and the PV. The total vascular enhancement associated with each test item was determined by the trapezoidal rule of area under the curve (AUC), where positive signal above y = 0 was included. From this, time-relative fractions at the arterial phase (AP: 30 secs), portal venous phase (PVP: 60 secs) and late venous phase (LVP: 120 secs) were expressed as a proportion of the total vascular AUC (%RVI) and were calculated as 1 - %RVI to give the percentage reduction though each phase.

[0083] For the delayed phase, a qualitative assessment was performed by an experienced radiologist for the presence or lack of enhancement pre and post-administration of test item.

[0084] *In vitro* relaxivities of test items

[0085] Combo 1, Combo 2 and Combo 3 were shown to have the expected relaxivities and r2/r1 ratios, based on the proportions of the various APIs(Table 2). The relaxivity measurements demonstrated all agents were viable and within standard relaxivity (r1) ranges.

[0086] Table 2 below shows the relaxivity (r1) and r2/r1 ratio measured in water at 37°C at 60MHz for each test item.

Test Item	Relaxivity ($mM^{-1}s^{-1}$) in aqueous solution	Ratio r2/r1
Gadoxetate	4.7	1.1
Gadoterate	2.9	1.1
Combo 1	3.3	1.2
Combo 2	3.5	1.2
Combo 3	3.7	1.2

HPLC analysis of test items.

Detector: ESA Corona, Charged Aerosol Detector and UV detector (280nm);
Column: SeQuant ZIC-pHILIC (5 µm, 150*4.6mm).

Sample preparation: to 30 µL test item was added $Mn(OAc)_2$ (10 µL, 10mg/mL) then MQ-water (360 µL) followed by MeCN (600 µL)*.
Injection volume: 20 µL;
Mobile phase: 100 mM ammonium acetate (A), Acetonitrile (B).
The column was conditioned with an initial composition (of 15:85 A:B) at a flow rate of 1mL/min for at least five minutes prior to sample injection.

Gradient:

	Time(min)	Flow Rate (mL/min)	%A	%B	Curve
1.	0	1.0	15	85	6
2.	40	1.0	30	70	6
3.	41	1.0	15	85	6
4	46	1.0	15	85	6

where curve 6 refers to a linear gradient.

The following retention times were observed:

	Retention time (min)
Meglumine	21.8
GdDOTA	23.5
Gd-EOB-DTPA	13.8
Na	17.5
Gd-BT-DO3A	24.2

* DOTA, EOB-DTPA and BT-DO3A were analysed indirectly as the corresponding Mn complexes.

Combo 1, Combo 2 and Combo 3 were shown to have expected API ratios in the HPLC analysis. The chemical integrity of the different APIs in the combo formulations was confirmed.

[0087] Quantitative analysis and signal intensity curves

[0088] For each test item, signal intensity (SI) curves were plotted for the aorta, IVC, PV and liver parenchyma ROIs as shown in Figure 3. Peak arterial enhancement was evident with all test items, with highest SI evident from Combo 1, Combo 2 and gadoterate (Table 3) Figures 3A-E respectively illustrate the peak SI curves for gadoxetate, gadoterate, Combo 1, Combo 2 and Combo 3. This indicates there is comparable early arterial enhancement with all agents, including the liver specific agent gadoxetate.

[0089] Table 3 below shows the peak signal intensity from the aorta with percentile range 25% to 75% and area under the curve (AUC) from the relative vascular index (RVI) curves for each test item.

Test Item	Gadoxetate	Gadoterate	Combo 1	Combo 2	Combo 3
Peak Aorta SI (25% - 75% Percentile)	2096 (467 - 1064)	2402 (225 -1169)	2926 (672 - 1669)	2485 (707 -1414)	2080 (554 - 1304)
RVI AUC	34.2 AU	63.2 AU	93.8 AU	76.7 AU	84.9 AU

[0090] Vascular intensity analysis

[0091] The RVI curves were calculated for each test item and the AUC is reported in Table 3

and composite vascular intensity curves were determined to profile each test item. Figures 4A-E respectively illustrate the RVI curves for gadoxetate, gadoterate, Combo 1, Combo 2 and Combo 3.

[0092] For each of the vascular phases (AP:30 secs, PVP: 60 secs, LVP: 120 secs), time-relative fraction was expressed as percentage relative vascular intensity (%RVI) of the total AUC for each test item (Figure 5, Table 4).

[0093] Table 4 below shows the dynamic vascular phases expressed as percentage relative vascular intensity (1 – RVI%) for the arterial phase (30 secs), the portal venous phase (60 secs) and the late venous phase (120 secs).

Vascular Phases	**Gadoxetate**	**Gadoterate**	**Combo 1**	**Combo 2**	**Combo 3**
AP (30 secs)	82.4%	97.5%	89.2%	90.0%	90.7%
PVP (60 secs)	19.0%	42.8%	51.2%	46.6%	42.7%
LVP (120 secs)	0.0%	8.4%	13.3%	10.8%	8.4%

[0094] Higher relaxation combo agent

[0095] Two different non-specific gadolinium based contrast agents were used in this study to formulate Combo 1, Combo 2 (gadoterate) and Combo 3 (gadobutrol). Both agents showed an increase of AUC in comparison to gadoterate alone and similar %RVI for each of the vascular phases.

[0096] Qualitative assessment for delayed enhancement phase

[0097] For the delayed phases, radiological assessment indicated adequate enhancement of the liver parenchyma for Combo 1, Combo 2 and Combo 3 in comparison to gadoxetate between pre and post administration of test item.

CLAIMS

1. A pharmaceutical preparation comprising:

(i) a first active pharmaceutical ingredient (API) having hepatocellular uptake and biliary excretion; and,

(ii) a second API having renal excretion;

wherein each of said first API and said second API is a metal chelate comprising a cheland or a derivative thereof and a paramagnetic metal ion, and wherein the ratio of said first API to said second API is from 1:10 to 4:1.

2. The pharmaceutical preparation as defined in Claim 1 wherein said paramagnetic metal ion is a transition metal or a lanthanide.

3. The pharmaceutical preparation as defined in Claim 2 wherein said paramagnetic metal ion is selected from the group comprising Eu, Gd, Dy, Ho, Cr, Mn and Fe.

4. The pharmaceutical preparation as defined in Claim 3 wherein said paramagnetic metal ion is selected from the group comprising Gd, Mn, Fe and Cr.

5. The pharmaceutical preparation as defined in Claim 4 wherein said paramagnetic metal ion is selected from the group comprising Gd(III) and Mn(II).

6. The pharmaceutical preparation as defined in Claim 5 wherein said paramagnetic metal ion is Gd(III).

7. The pharmaceutical preparation as defined in any one of Claims 1-6 wherein said cheland or derivative thereof is selected from the group comprising: diethylenetriaminepentaacetic acid (DTPA); 4-carboxy-5, 8, 11-tris(carboxymethyl)-1-phenyl-2oxa-5, 8, 11-triazatridecan-13-oic acid (BOPTA);; 1, 4, 7, 10-tetraazacyclododecan-1, 4, 7-triactetic acid (DO3A),); 1, 4, 7, 10-tetraazacyclododecan-1, 4, 7, 10-tetraactetic acid (DOTA); ethylenediaminotetraacetic acid (EDTA); 10-(2-hydroxypropyl)-1, 4, 7, 10-tetraazacyclododecan-1, 4, 7-triacetic acid (HP-DO3A); 2-methyl-1, 4, 7, 10-tetraazacyclododecan-1, 4, 7, 10-tetraacetic acid (MCTA); tetramethyl-1, 4, 7, 10-tetraazacyclododecan-1, 4, 7, 10-tetraacetic acid (DOTMA); 3, 6, 9, 15-tetraazabicyclo[9.3.1]pentadeca-1(15), 11, 13-triene-3, 6, 9-triacetic acid (PCTA),); N, N'Bis(2-aminoethyl)-1,2-ethanediamine (TETA); 1,4,7,10-tetraazacyclotridecane- N,N',N'',N'''-tetraacetic

acid (TRITA),); 1,12-dicarbonyl, 15-(4-isothiocyanatobenzyl) 1, 4, 7, 10, 13-pentaazacyclohexadecane-N, N', N" triaceticacid (HETA); [(2S,5S,8S,11S)-4,7-bis-carboxymethyl-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclo-dodecan-1-yl]acetic acid, (M4DO3A); 1 1-O-Phosphonomethyl- 1,4,7, 1-O-tetraazacyclododecane- 1,4,7-triacetic acid (MPDO3A),); hydroxybenzyl-ethylenediamine-diacetic acid (HBED); and, N,N'-ethylenebis-[2-(o-hydroxyphenolic)glycine](EHPG); 2-[[2-[bis(carboxylatomethyl)amino]-3-(4-ethoxyphenyl)propyl]-[2-[bis(carboxylatomethyl)amino]ethyl]amino]acetate (EOB-DTPA); 10–[(1SR,2RS)–2,3–dihydroxy–1–hydroxymethylpropyl]–1,4,7,10– tetraazacyclododecane–1,4,7–triacetic acid (BT-DO3A); 2-[bis[2-[carboxylatomethyl-[2-(methylamino)-2-oxoethyl]amino]ethyl]amino]acetate (DTPA-BMA); and, 2-[bis[2-[carboxylatomethyl-[2-(2-methoxyethylamino)-2-oxoethyl]amino]ethyl]amino]acetate (DTPA-BMEA); N-[2-[bis(carboxymethyl)amino]-3-(4-ethoxyphenyl)propyl]-N-[2-[bis(carboxymethyl)-amino]ethyl]-L-glycine (EOB-DTPA), N,N-bis[2-[bis(carboxymethyl)amino]-ethyl]-L-glutamic acid (DTPA-Glu), N,N-bis[2-[bis(carboxymethyl)amino]-ethyl]-L-lysine (DTPA-Lys), N,N-bis[2-[carboxymethyl[(methylcarbamoyl)methyl]amino]-ethyl] glycine (DTPA-BMA); 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid mono-(N-hydroxysuccinimidyl) ester (DOTA-NHS); [(2S,5S, 8S, 11S)-4,7,10-tris-carboxymethyl-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecan-1-yl]acetic acid (M4DOTA); (R)-2-[(2S,5S,8S,11S)-4,7,10-tris-((R)-1-carboxyethyl)-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecan-1-yl]propionic acid (M4DOTMA); PCTA12; cyclo-PCTA12; N, N'-Bis(2-aminoethyl)-1,2-ethanediamine-N-hydroxy-succinimide ester (TETA-NHS).

8. The pharmaceutical preparation as defined in Claim 7 wherein said cheland or derivative thereof is selected from EOB-DTPA, DTPA-BMA, DTPA-BMEA, DTPA, DOTA, BOPTA, HP-DO3A, BT-DO3A.

9. The pharmaceutical preparation as defined in any one of Claims 1-8 wherein the ratio of said first API to said second API is from 1:5 to 3:2.

10. The pharmaceutical preparation as defined in Claim 9 wherein the ratio of said first API to said second API is from 1:4 to 1:1.

11. The pharmaceutical preparation as defined in Claim 10 wherein the ratio of said first API to said second API is 1:1.

12. The pharmaceutical preparation as defined in Claim 10 wherein the ratio of said first API to said second API is 1:2.

13. The pharmaceutical preparation as defined in Claim 10 wherein the ratio of said first API to said second API is 1:3.

14. The pharmaceutical preparation as defined in Claim 10 wherein the ratio of said first API to said second API is 1:4

15. The pharmaceutical preparation as defined in any one of Claims 1-14 wherein said first API is gadoexetate.

16. The pharmaceutical preparation as defined in any one of Claims 1-15 wherein said second API is selected from the group comprising gadodiamide, gadoversetamide, gadolinium diethylene triamine pentaacetic acid, gadoteridol, gadobutrol, gadobenate dimeglumine, and gadoterate meglumine.

17. The pharmaceutical preparation as defined in Claim 16 wherein said second API is selected from the list comprising gadoteridol, gadobutrol and gadoterate meglumine.

18. The pharmaceutical preparation as defined in any one of Claims 1-17 wherein said first API and said second API are provided separately but configured to permit simultaneous administration.

19. The pharmaceutical preparation as defined in any one of Claims 1-18 wherein each of said first API and said second API are provided as a pharmaceutical composition together with a biocompatible carrier in a form suitable for mammalian administration.

20 The pharmaceutical preparation as defined in any one of Claims 1-17 which is provided as a pharmaceutical composition wherein said first API and said second API are formulated together with a biocompatible carrier in a form suitable for mammalian administration.

21. The pharmaceutical preparation as defined in either Claim 19 or Claim 20 wherein said pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

22. The pharmaceutical preparation as defined in Claim 21 wherein said one or more pharmaceutically acceptable excipients comprises a buffering agent.

23. The pharmaceutical preparation as defined in Claim 21 wherein said one or more pharmaceutically acceptable excipients comprise excess cheland.

24. The pharmaceutical preparation as defined in any one of Claims 20-23 wherein gadoexetate and gadoterate meglumine are formulated together with an excess of the free acid of EOB-DTPA, and wherein meglumine is a sole buffering agent.

25. A dose of a pharmaceutical preparation to be administered to a subject wherein said pharmaceutical preparation is as defined in any one of Claims 1-24 and wherein said dose comprises between 0.01-0.04 mmol per kilogram of said subject of said first API and between 0.01-0.1 mmol *per* kilogram of said subject of said second API with the proviso that the combined dose of said first API and second API does not exceed 0.125 mmol *per* kilogram of said subject.

26. The dose as defined in Claim 25 wherein the combined dose of said first API and second API is less than 0.125 mmol per kilogram of said subject.

27. The dose as defined in either Claim 25 or Claim 26 which comprises between 0.02-0.03 mmol *per* kilogram of said subject of said first API.

28. The dose as defined in any one of Claims 25-27 which comprises between 0.025-0.1 mmol *per* kilogram of said subject of said second API wherein said second API has a relaxivity $\geq$ 3 mM-1s-1 at field strengths of 1.5-3 T.

29. The dose as defined in Claim 28 wherein said dose comprises:

0.02 mmol *per* kilogram of said subject of said first API and between 0.04-0.1 mmol *per* kilogram of said subject of said second API; or,

0.02 mmol *per* kilogram of said subject of said first API and between 0.05-0.1 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.03-0.1 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.04-0.1 mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.025-0.1

mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.04-0.095 mmol *per* kilogram of said subject of said second API.

30. The dose as defined in any one of Claims 25-27 which comprises between 0.02-0.09 mmol *per* kilogram of said subject of said second API wherein said second API has a relaxivity ≥ 5 mM-1s-1 at field strengths of 1.5-3 T.

31. The dose as defined in Claim 30 wherein said dose comprises:

0.02 mmol *per* kilogram of said subject of said first API and between 0.03-0.09 mmol *per* kilogram of said subject of said second API; or,

0.02 mmol *per* kilogram of said subject of said first API and between 0.04-0.09 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.025-0.09 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.03-0.08 mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.02-0.09 mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.03-0.075 mmol *per* kilogram of said subject of said second API.

32. The dose as defined in any one of Claims 25-27 which comprises between 0.02-0.07 mmol *per* kilogram of said subject of said second API wherein said second API has a relaxivity ≥ 7 mM-1s-1 and field strengths of 1.5-3 T.

33. The dose as defined in Claim 32 wherein said dose comprises:

0.02 mmol *per* kilogram of said subject of said first API and between 0.02-0.07 mmol *per* kilogram of said subject of said second API; or,

0.02 mmol *per* kilogram of said subject of said first API and between 0.03-0.06 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.02-0.07 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.025-0.06 mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.02-0.06 mmol *per* kilogram of said subject of said second API.

34. The dose as defined in any one of Claims 25-27 which comprises between 0.01-0.06 mmol *per* kilogram of said subject of said second API wherein said second API has a relaxivity $\geq$ 9 mM-1s-1 at field strengths of 1.5-3 T.

35. The dose as defined in Claim 34 wherein said dose comprises:

0.02 mmol *per* kilogram of said subject of said first API and between 0.02-0.06 mmol *per* kilogram of said subject of said second API; or,

0.02 mmol *per* kilogram of said subject of said first API and between 0.02-0.05 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.02-0.06 mmol *per* kilogram of said subject of said second API; or,

0.025 mmol *per* kilogram of said subject of said first API and between 0.02-0.05 mmol *per* kilogram of said subject of said second API; or,

0.03 mmol *per* kilogram of said subject of said first API and between 0.01-0.05 mmol *per* kilogram of said subject of said second API.

36. The dose as defined in any one of Claims 25-35 which comprises 0.025 mmol *per* kilogram of said subject of said first API.

37. The dose as defined in any one of Claims 25-36 which comprises 0.1 mmol *per* kilogram of said subject of said second API.

38. The dose as defined in any one of Claims 25-36 which comprises 0.05 mmol *per* kilogram of said subject of said second API.

39. The dose as defined in any one of Claims 25-38 wherein said subject is a living human or

non-human animal body.

40. A method comprising:

(a) administering a dose of a pharmaceutical composition to a subject wherein said dose is as defined in any one of Claims 25-39;

(b) carrying out magnetic resonance imaging (MRI) on said subject following said administering step wherein magnetic resonance (MR) signals are detected from the subject or parts of the subject into which the composition has distributed;

(c) generating MR images and/or MR spectra from the detected MR signals.

41. The method as defined in Claim 40 wherein said subject is a living human or non-human animal body.

42. The method as defined in either Claim 40 or Claim 41 wherein said composition is administered in an amount suitable to enhance the contrast in the method of MR imaging.

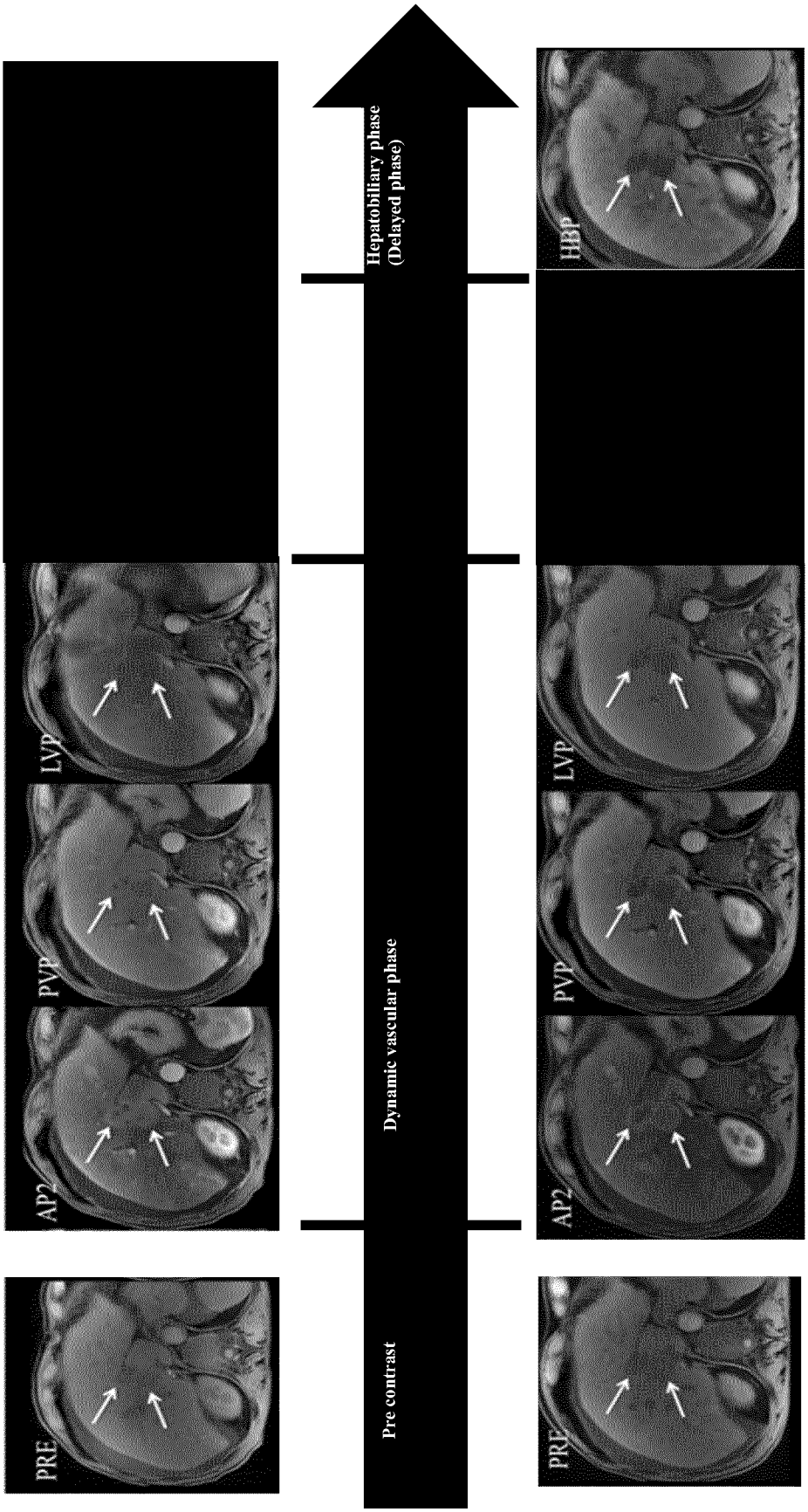

PRE
AP2
PVP
LVP
HBP
Pre contrast
Dynamic vascular phase
Hepatobiliary phase
(Delayed phase)

Figure 1

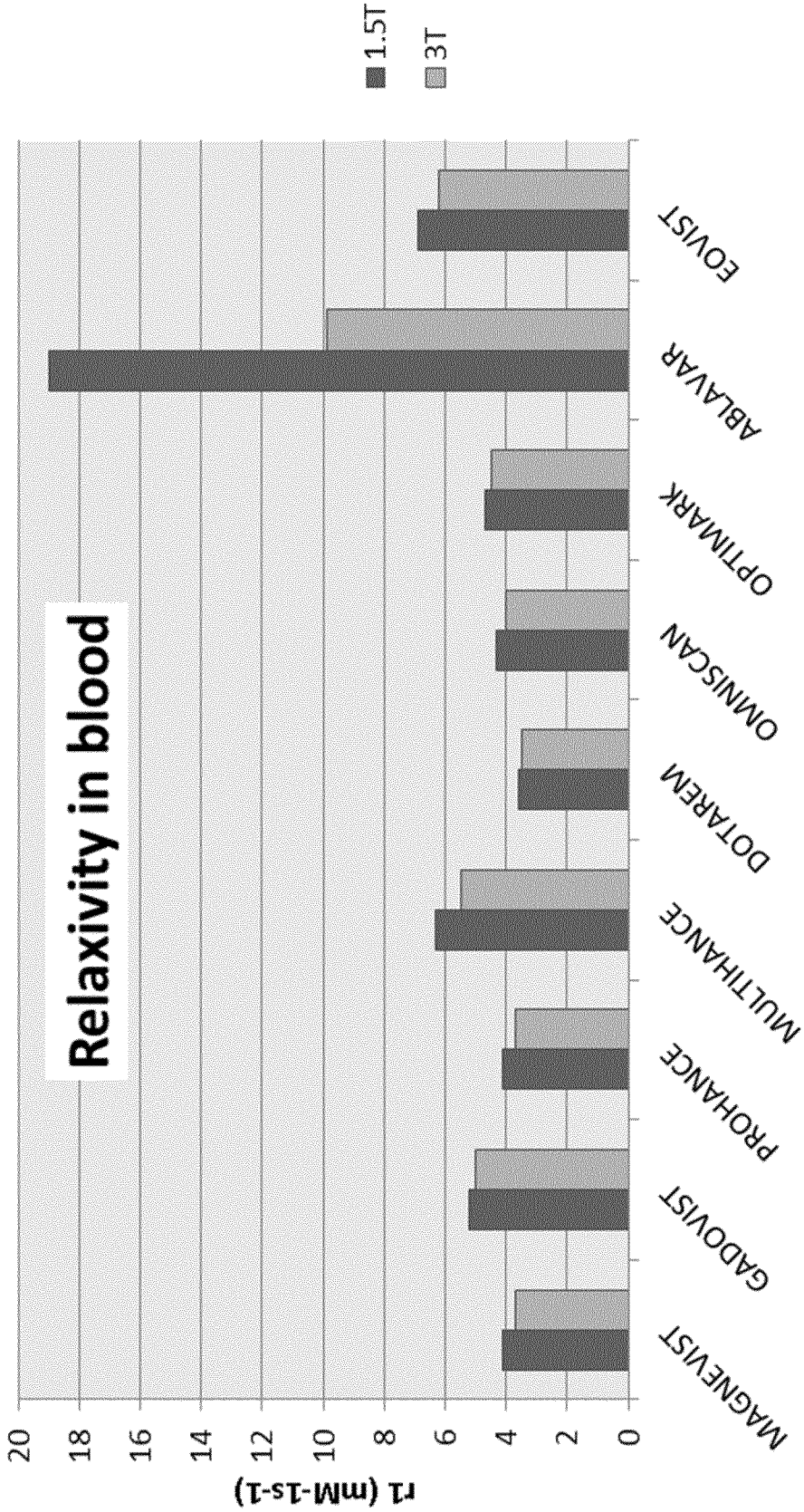
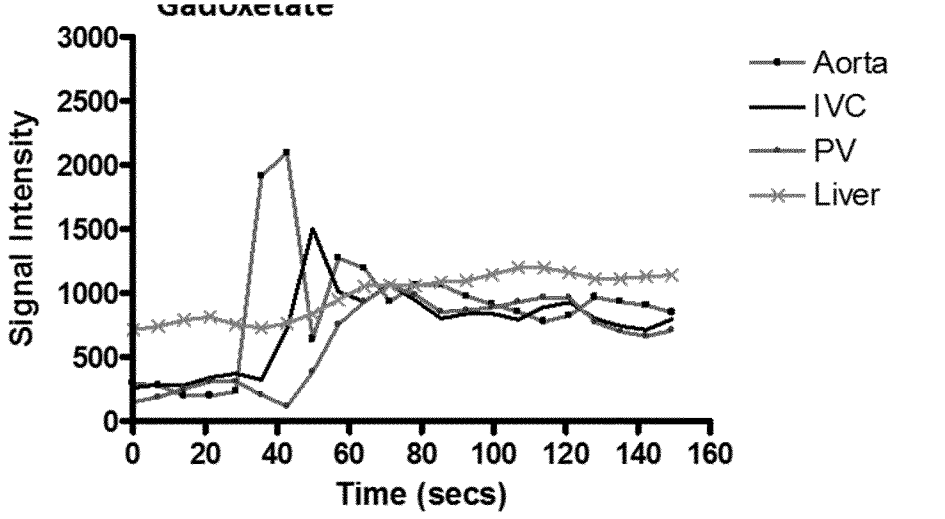
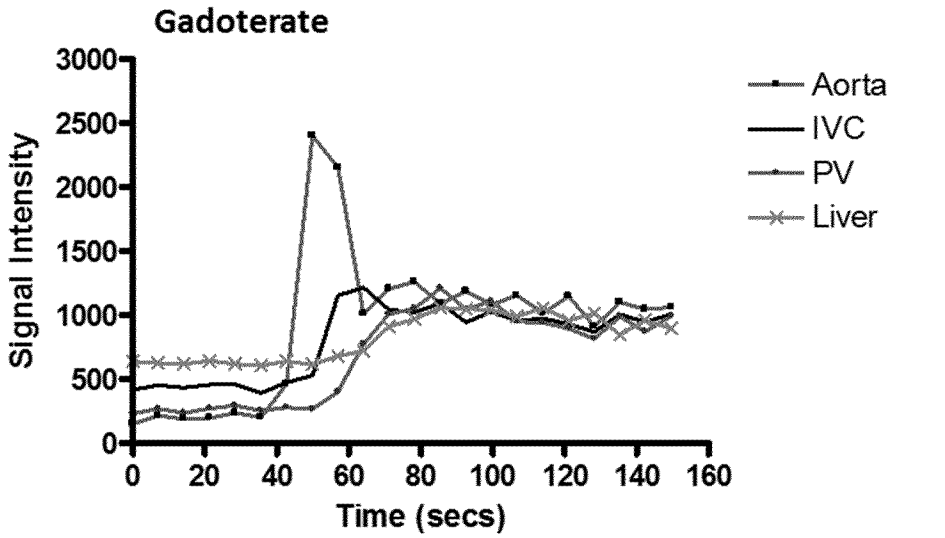

Relaxivity in blood
1.5T
3T
r1 (mM-1s-1)
0
2
4
6
8
10
12
14
16
18
20
MAGNEVIST
GADOVIST
PROHANCE
MULTIHANCE
DOTAREM
OMNISCAN
OPTIMARK
ABLAVAR
EOVIST

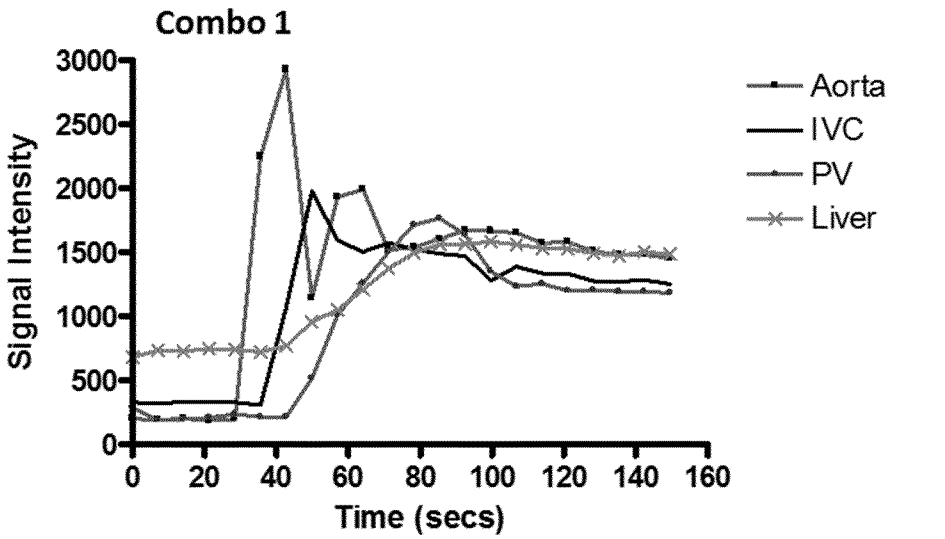
Figure 2



A

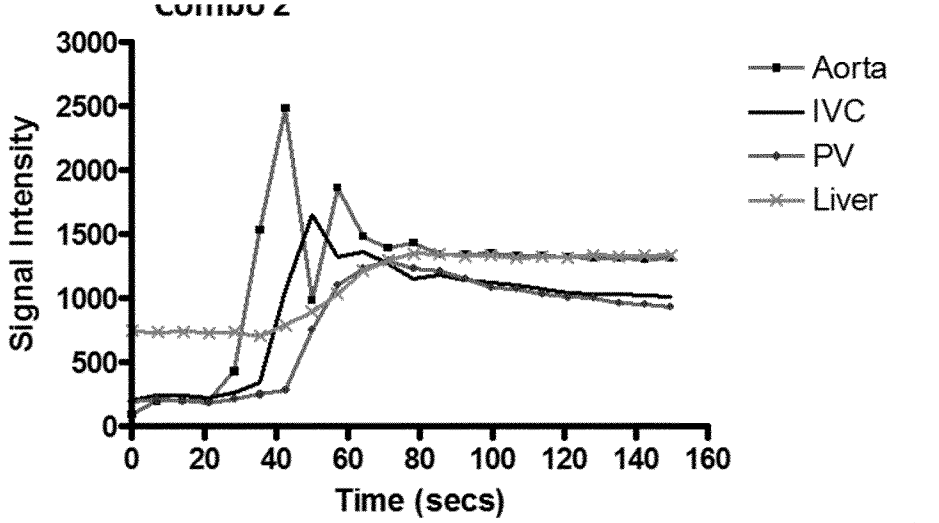


B

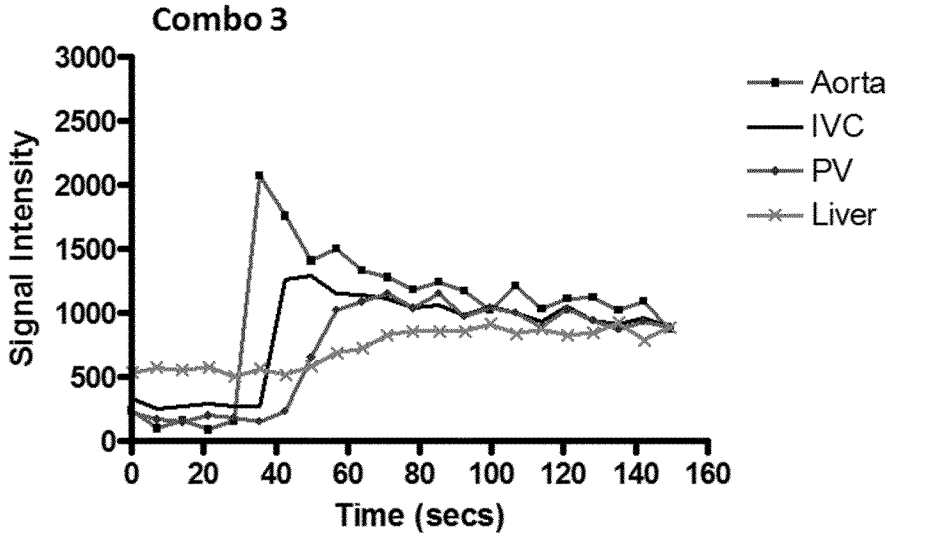


C

Figures 3A-C



D



E

Figures 3D-E

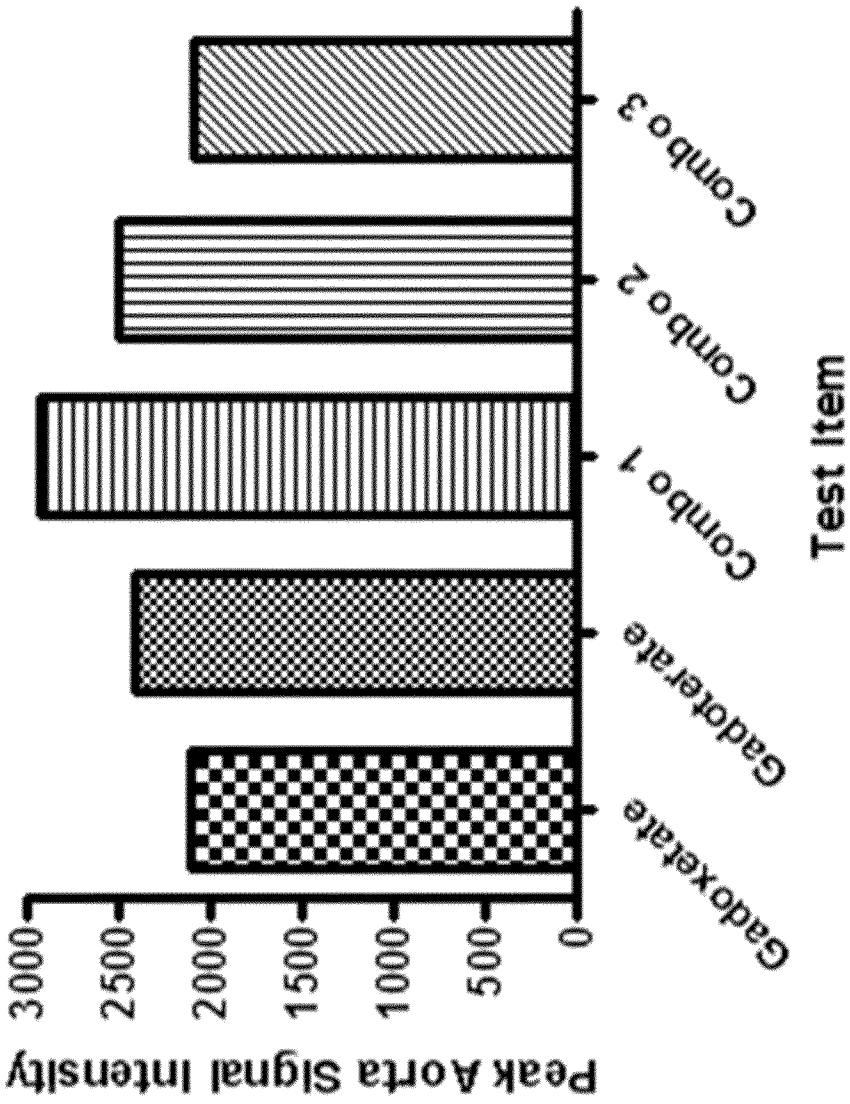
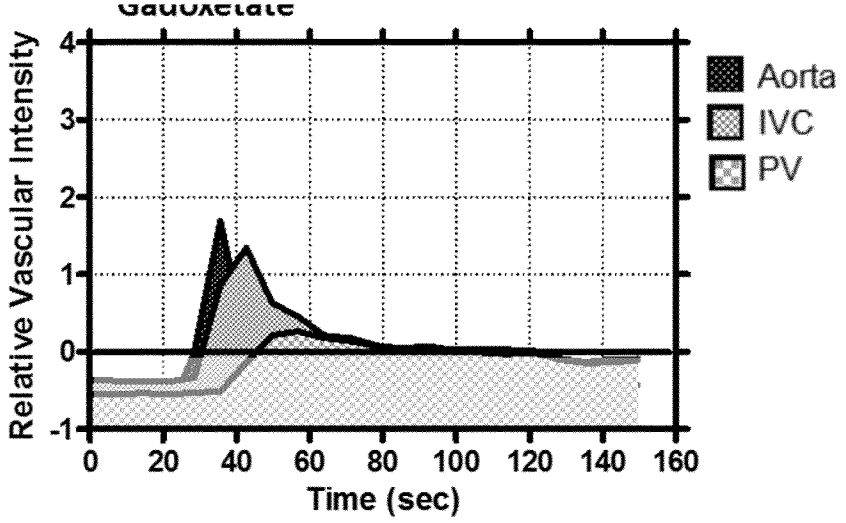
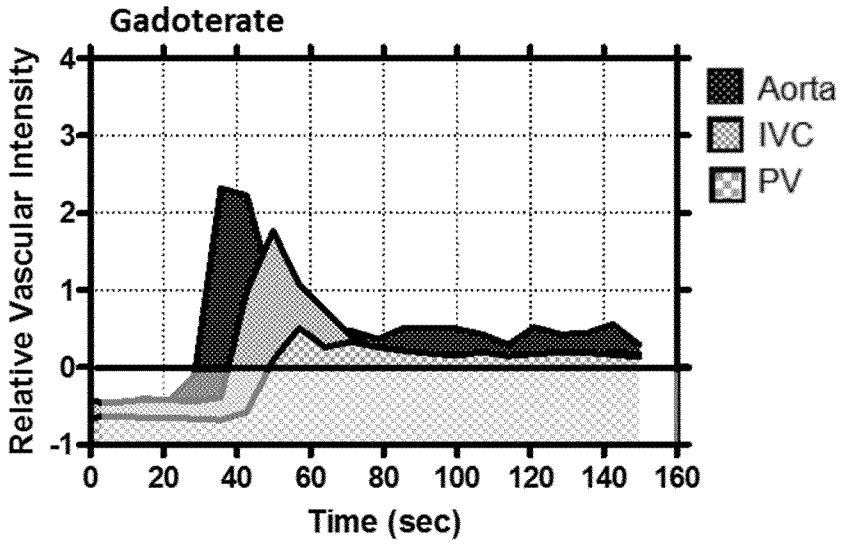

Peak Aorta Signal Intensity
3000
2500
2000
1500
1000
500
0
Gadoxetate
Gadoterate
Combo 1
Combo 2
Combo 3
Test Item

Figure 3F



A



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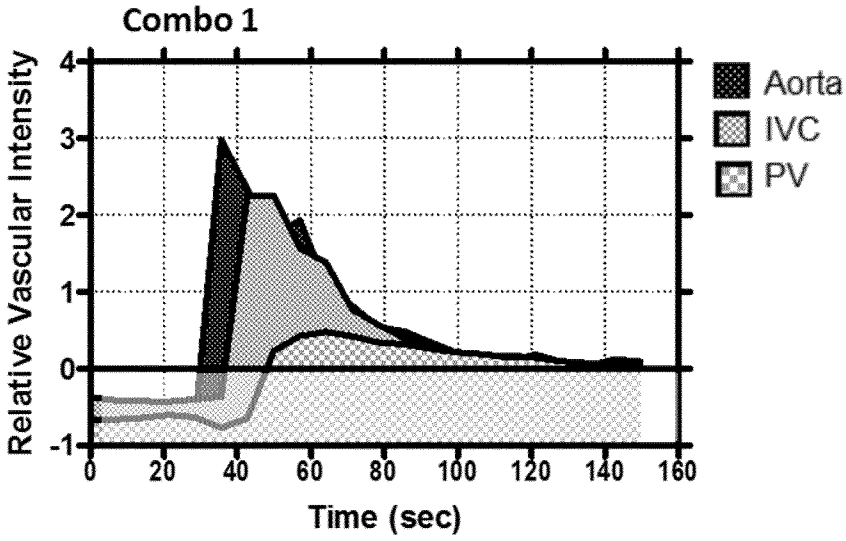
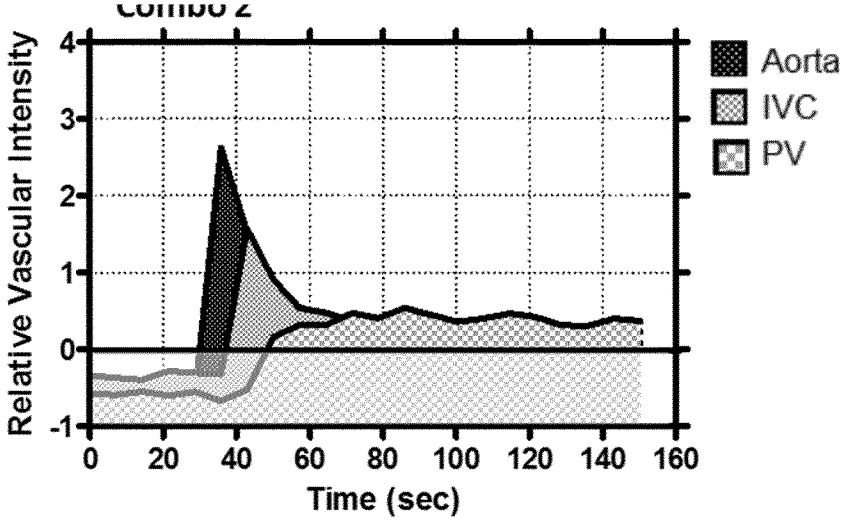
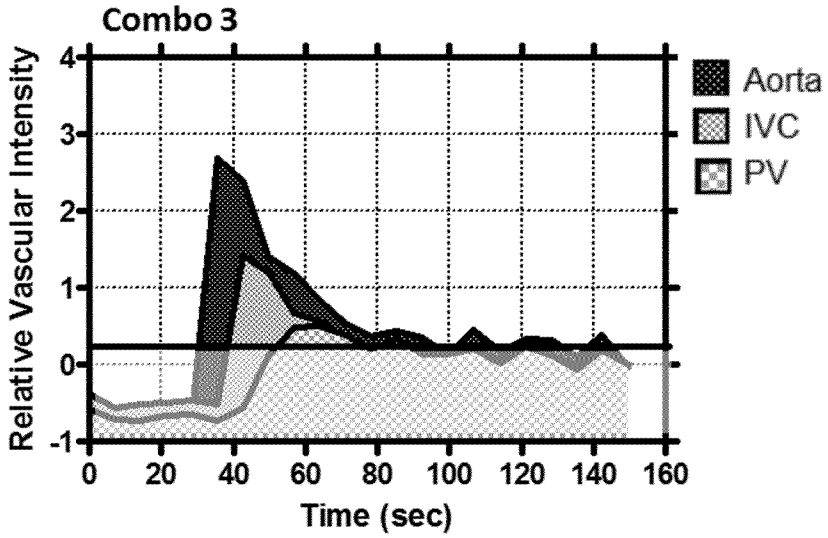


C

Figure 4A-C



D



E

Figure 4D-E

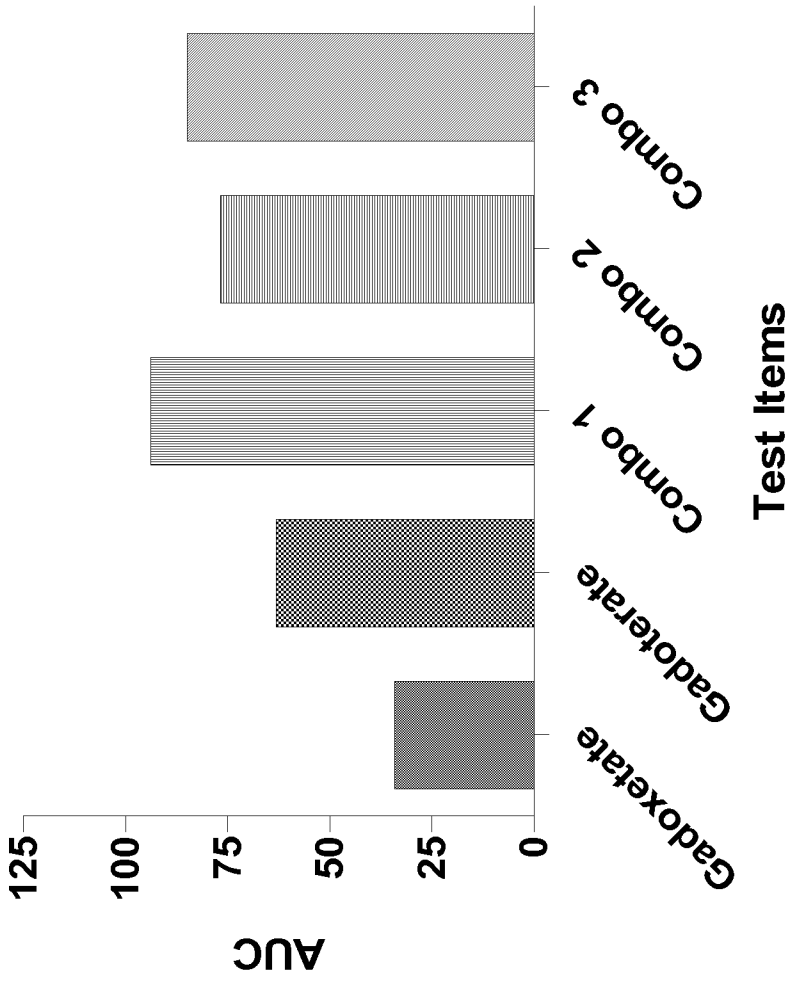

AUC
125
100
75
50
25
0
Gadoxetate
Gadoterate
Combo 1
Combo 2
Combo 3
Test Items

Figure 4F

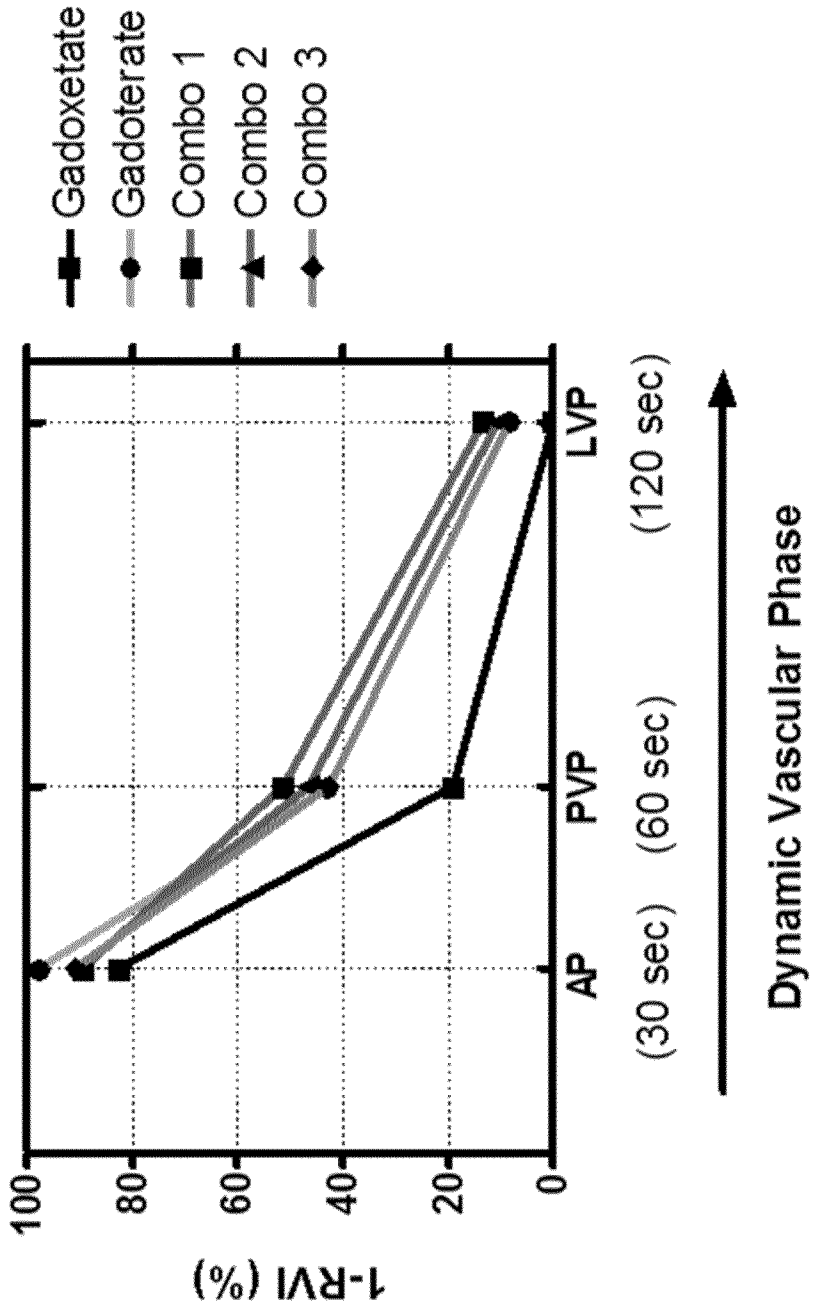

Gadoxetate
Gadoterate
Combo 1
Combo 2
Combo 3
1-RVI (%)
100
80
60
40
20
0
AP
PVP
LVP
(30 sec)
(60 sec)
(120 sec)
Dynamic Vascular Phase

Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/079311

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K49/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DUPAS BENOIT ET AL: "Delineation of Liver Necrosis Using Double Contrast-Enhanced MRI", JOURNAL OF MAGNETIC RESONANCE IMAGING, SOCIETY FOR MAGNETIC RESONANCE IMAGING, OAK BROOK, IL, US, vol. 7, no. 3, 1 January 1997 (1997-01-01) , pages 472-477, XP002094271, ISSN: 1053-1807	1-3, 7-14, 18-22
Y	page 472, column 2, line 1 - page 473, column 1, line 16 page 474, column 1, line 6 - column 2, line 12 page 476, column 2, line 37 - page 477, column 1, line 25	23,25-42

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
7 February 2017	16/02/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Jetter, Sonya

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/079311

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	KRISHNA KATTEL ET AL: "Paramagnetic dysprosium oxide nanoparticles and dysprosium hydroxide nanorods asMRI contrast agents", BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 33, no. 11, 4 January 2012 (2012-01-04), pages 3254-3261, XP028414066, ISSN: 0142-9612, DOI: 10.1016/J.BIOMATERIALS.2012.01.008 [retrieved on 2012-01-07] page 3260, column 1, line 9 - page 3261, column 1, line 7	1-42
A	AHMED BA-SSALAMAH ET AL: "Clinical value of MRI liver-specific contrast agents: a tailored examination for a confident non-invasive diagnosis of focal liver lesions", EUROPEAN RADIOLOGY, SPRINGER, BERLIN, DE, vol. 19, no. 2, 23 September 2008 (2008-09-23), pages 342-357, XP019709456, ISSN: 1432-1084 page 343, column 1, line 23 - column 2, line 14; figure 16	1-42
X	R. GOLFIERI ET AL: "Ruolo della RM a doppio contrasto rispetto alla TC multidetettore nella diagnosi del piccolo epatocarcinoma (<=3 cm) su cirrosi", RADIOLOGIA MEDICA., vol. 114, no. 8, 20 August 2009 (2009-08-20), pages 1239-1266, XP55341409, IT ISSN: 0033-8362, DOI: 10.1007/s11547-009-0439-x	1-4
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