CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-090

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA	22-090	*Submission Date*	June 29, 2007
Brand Name		Gd-EOB-DTPA	
Generic Name		Primovist	
Reviewer		Christy S. John, Ph.D	
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OCP Division		V	
ORM Division		Division of Medical Imaging and Hematology Drug Products	
Sponsor		Bayer Health Care Pharmaceuticals, Inc.	
Relevant IND(s)		54,875	
Submission Type; Code		S	1
Formulation; Strength(s)		PRIMOVIST is provided in a concentration of 0.25 mmol/ml of gadoxetic acid, disodium (formulation code number SH L569B). Each ml of this formulation contains 181.43 mg of Gd-EOB-DTPA.	
Proposed Indication		Primovist® Injection is indicated for use in magnetic resonance imaging (MRI) of the liver in adult patients [redacted] the T1-weighted images [redacted] detection, [redacted] and characterization of focal liver pathologies ([redacted], in a pre-surgical evaluation.	
Proposed Dose		0.25 mmol/kg body weight intravenous injection	

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1 Executive Summary

Gd-EOB-DTPA (Primovist) is a Gadolinium-based T1 MR-contrast agent for imaging focal liver lesion including benign (cysts, hemangioma, etc) and malignant lesions (hepatocellular carcinoma). Chemically, Gd-EOB- DTPA is a derivative of Gd-DTPA. A lipophilic moiety was added which results in a weak protein binding and enables Gd-EOB-DTPA to enter the hepatocytes via membrane bound carriers (organic anion transporting polypeptides, OATPs). Excretion into the bile is mediated by the energy dependent organic anion transporter.

The analysis of pharmacokinetic parameters was performed using a 2-compartment model. Gd was eliminated from plasma in a biphasic manner. The half-lives of Phase I and Phase II were 0.11 to 0.21 hr and 1.3 to 1.6 hr, respectively. The AUC increased dose-dependently, and there was a linear relationship between dose and AUC in the dose range from 25 to 100 µmol Gd/kg. No marked difference between the doses was observed in any other parameters.

The dose selection for Phase III clinical trial was based on two clinical trials. One used the signal intensity in the liver as compared to smooth muscle. This study used four doses 10, 25, 50 and 100 µmol/kg of body weight. A dose dependent increase in relative signal intensity and AUC in liver was observed up to 50 µmol/kg. Another phase II study was performed for the dose selection where a change in diagnostic confidence was used as primary endpoint. The doses studied were 3, 6, 12.5 and 25 µmol/kg. The dose recommended for Phase III clinical studies (25 µmol/kg) gave a 50-55% increase in signal intensity in the lesion free portion of the liver.

Pharmacokinetics in patients with moderate renal impairment, moderate hepatic impairment, and concurrent moderate renal plus moderate hepatic impairment were similar. In elderly (>65 yr) patients, CL(total) was 22% lower and terminal $t_{1/2}$ was 43 % higher, compared to non-elderly (<65 yr) patients. In female patients, CL(total) was 22% lower compared to male patients.

The pharmacokinetic parameters derived from serum concentration data of Gd-EOB-DTPA were not markedly altered in special population except in end stage renal failure (ESRF) patients. **Pharmacokinetics of Gd-EOB-DTPA were markedly different in ESRF. Total clearance was only 17%,**

terminal half-life was about 12-fold longer, and extent of fecal excretion was relatively higher compared to patients with normal renal function. Based upon the prolonged biological half-life of primovist in ESRF patients and in severe renal impaired patients, the possibility of significant toxicity cannot be ruled out in this patient population.

The results of studies in laboratory animal models indicated that the organic anion transporting polypeptides (OATP) and energy dependent organic anion transporter (cMOAT) are involved in Gd-EOB-DTPA uptake into hepatocytes and subsequent excretion into the bile. The sponsor did not investigate the effect of OATP inhibitors on the hepatic uptake of primovist. However, it is shown in pre-clinical studies that a high dose of rifampicin (an OATP inhibitor) could inhibit the uptake of primovist in liver. **Therefore, it is recommended that the patients undergoing primovist administration should avoid taking rifamycin. The sponsor is required to study the effect of rifamycin or other OATP inhibitors on the hepatic uptake of primovist as a post marketing commitment.**

1.1.1 Recommendations:

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V has reviewed NDA 22-090. The application is acceptable from a clinical pharmacology perspective provided the recommendations (as shown in detail labeling recommendations) of clinical pharmacology review are incorporated in the label and the Phase 4 study commitment is accepted by the Applicant.

1.2 Phase IV Commitment:

The sponsor is requested to commit to study the effect of rifamycin or other OATP inhibitors on the hepatic uptake of Gd-EOB-DTPA in a post marketing commitment, if the drug is approved for marketing.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings:

Gd-EOB-DTPA is a MRI contrast agent for imaging malignant and benign tumors of the liver. The results of the laboratory experiments showed that Gd-EOB-DTPA has the following characteristics: a) high relaxivity, b) extremely high complex stability, c) lack of biotransformation, d) active hepatic uptake, e) excretion in to the bile of a large portion of the dose and, f) <10% protein binding.

After bolus injection (dose, 10 – 100 µmol /kg BW), the rapid removal of Gd-EOB-DTPA from the circulation was attributed to uptake by the liver and a rapid renal elimination. Although the hepatic uptake and disposition of Gd-EOB-DTPA is known to be mediated by an active carrier, mean terminal half-life (range, 1.1 - 1.6 h), and total clearance (range, 224 - 272 mL/min) remained unchanged, as well as the fecal and urinary excretion (50: 50 proportion) up to a 4-fold higher dose than the suggested clinical dose, indicating that disposition processes are not saturated. Rapid and efficient urinary excretion and a dose independent renal clearance at a dose 20-fold higher than the suggested clinical dose, were indicative of the governing role of renal elimination in the pharmacokinetics of Gd-EOB-DTPA.

Out of all the special population variables investigated (hepatic impairment, renal impairment, end stage renal failure, coexistent renal and hepatic impairment, gender and age) only the end stage renal failure (ESRF) had the most remarkable influence on the pharmacokinetics of Gd- EOB-DTPA. In the ESRF subjects, the terminal half-life was remarkably longer (20.4 h compared to < 3 h in all other groups studied) and the systemic exposure was higher (AUC was 5.6-fold higher in ESRF compared to the control group) (Table I). **Gd-EOB-DTPA is a structurally similar analog of Magnevist. The basic chelating entity for primovist is the same (DTPA) as magnevist. There are at least 15 cases of nephrogenic systemic fibrosis (NSF) reported in the AERS for Magnevist. The current scientific understanding is that there is de-complexation of free Gd+3 ions from the chelate that gives rise to NSF. The boxed warning on primovist label (and all Gd contrast agents) for NSF will discourage physicians from using primovist in patients with severe renal impairment and in patients with end stage renal failure.**

Moderate renal impairment (GFR, 30 – 50 mL/min) and severe hepatic impairment (Child-Pugh category C) had a modest effect on pharmacokinetic variables derived from the serum levels. Compared to the control group, in moderate renal impairment and in severe hepatic impairment, the mean total clearance decreased by 28% and 33%, mean total AUC increased by 48% and 60%, respectively, and the terminal half-life increased slightly as shown in Table I. Fecal excretion was decreased in severe hepatic impairment (mean, 5.7% of the dose), more remarkably in patients with >3 mg/dL serum bilirubin (< 0.5% of the dose in the feces). A compensatory shift in the extent of urinary excretion was observed (mean urinary excretion of 61.3% in the severe hepatic impairment, and > 72% urinary excretion in patients with serum bilirubin >3 mg/dL).

Table I. Summary of comparison of pharmacokinetic parameters of Gd-EOB-DTPA in moderately and severely renal impaired patients after intravenous bolus injection (values are in comparison to control).

Parameter	Severity of Renal Impairment	Change Compared to Normal Controls
AUC	Moderate	1.5 fold increase
	Severe (ESRD)	5.6 fold increase
CLtot	Moderate	28% decrease
	Severe	83% decrease
$T_{1/2}$	Moderate	1.2 fold increase
	Severe (ESRD)	11.6 fold increase

Gd-EOB-DTPA was found to be dialyzable. In a 3-hour dialysis session, which started 1 hour after the administration of the dose, about 30 % of the Gd-EOB-DTPA dose was removed by dialysis.

2.0 Question Based Review

2.1. General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of Primovist?

An original IND was filed by the sponsor on December 19, 1997. After submitting the Gd-EOB-DTPA Injection IND in December 1997, Bayer HealthCare Pharmaceuticals (at that time Berlex) initiated the discussion of the clinical development plan with the FDA in January 1998 before starting the phase 3 trials. As a result, Bayer HealthCare Pharmaceuticals conducted an additional clinical study in special patient populations in the US as requested by the FDA.

In Europe, the product under evaluation, Gd-EOB-DTPA (Primovist) was first approved in Sweden in March 2004, with subsequent approval via Mutual Recognition Procedure in 25 EU countries for the indication "Primovist is indicated for the detection of focal liver lesions and provides information on the character of lesions in T1-weighted magnetic resonance imaging (MRI). This medicinal product is for diagnostic use by intravenous administration only". Gd-EOB-DTPA (Primovist) is approved in 34 countries, including the extended EU, Switzerland, Australia, South Africa and several Asian countries.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product as they relate to the clinical pharmacology of the drug?

PRIMOVIST (Gd-EOB-DTPA) is an intravenous contrast agent developed by Bayer Schering Pharma AG (Bayer Schering Pharma AG, Berlin, Federal Republic of Germany) for magnetic resonance imaging (MRI) of the liver and biliary system. The drug substance gadoxetate disodium (Gd-EOB-DTPA, gadolinium-EthOxyBenzyl- DiethyleneTriaminePentaAcid, ZK139834) is the disodium salt of the gadolinium complex of (S)-N-[2-[bis(carboxymethyl)amino]-3-(4-ethoxyphenyl) propyl]-N-[2-[bis(carboxymethyl) amino]ethyl]glycine.

The drug product PRIMOVIST is a sterile, injectable, ready to use, clear, colorless to slightly yellowish aqueous solution. PRIMOVIST is provided in a concentration of 0.25 mmol/ml of gadoxetic acid, disodium (formulation

code number SH L569B). Each ml of this formulation contains 181.43 mg of Gd-EOB-DTPA. PRIMOVIST will be presented in [redacted] 10 ml vials filled with [redacted] 10 ml.

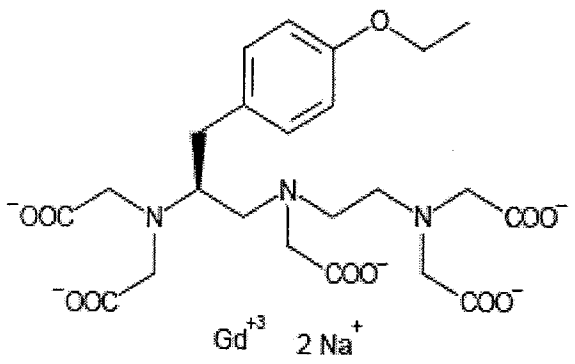

Figure I. Chemical Structure of Gadoxetate disodium (primovist)

Table II. Chemical composition of primovist.

The composition of 1 mL of Primovist (0.25 mmol/mL) contains the following:

No.	Name of Ingredient	Unit	Function	Refer to Standards
Active substances:				
1.	Gadoxetate disodium	181.430 mg	Active ingredient	---
Excipients:				
1.	Caloxetate trisodium	[redacted]		---
2.	Tromethamine	[redacted]		USP
3.	Hydrochloric acid w)	[redacted]	pH adjustment	NF
4.	Sodium hydroxide ad pH [redacted]	[redacted]	pH adjustment	NF
5.	Water for injection ad	[redacted]	Solvent	USP

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication?

Primovist is indicated for the detection of focal liver lesions and provides information on the character of lesions in T1-weighted magnetic resonance imaging (MRI). Gd-EOB-DTPA is a Gd-based T1 MR-contrast agent. Its mode of action is through shortening of the T1 relaxation time of hydrogen protons by the gadolinium which causes a significant increase of signal intensity in T1 weighted imaging sequences.

Chemically, Gd-EOB- DTPA is a derivative of Gd-DTPA. A lipophilic moiety was added which results in a weak protein binding and enables Gd-EOB-DTPA to enter the hepatocytes via membrane bound carriers (organic anion transporting polypeptides). Excretion into the bile is mediated by the energy dependent canalicular multispecific organic anion transporter. These properties result in a higher plasma relaxivity of Gd-EOB-DTPA as compared to available extracellular contrast agents. The relaxivity after uptake by hepatocytes goes up further which together allows for a reduction of the Gadolinium dose by a factor of 4 when compared to other extracellular contrast agents, i.e. only 25 µmol/kg bw is needed instead of 100 µmol/kg bw of a standard extracellular MR contrast agent (such as Magnevist or Omniscan). The dual excretion route of 50% renal and 50% biliary excretion may be and additional favorable feature for certain risk patients such as renally impaired patients.

2.1.4. What are the proposed dosage(s) and route(s) of administration?

A clinical dose of 25 µmol/kg body weight has been proposed via an intravenous injection. This dose is lower by a factor of four when compared with other approved gadolinium extracellular contrast agents where a dose of 0.1 mmol/kg is the approved dose.

2.2 General Clinical Pharmacology

A total of five clinical studies involving 160 healthy subjects / patients contribute to the Clinical Pharmacology (Pharmacokinetics and Pharmacodynamics) data base of Gd-EOB-DTPA. Out of the 160, 136 received single doses of Gd-EOB-DTPA (dose range 10 to 500 µmol/kg bw) and 24 received placebo. Of the 136 who received Gd-EOB-DTPA, 119 were males and 17 were females. Out of these five clinical studies three

studies (two conducted in Germany and one conducted in Japan) provide pharmacokinetic data (serum levels and urinary and fecal excretion) in healthy male volunteers and cover a dose range of 10 to 500 µmol Gd-EOB-DTPA per kg body weight.

Following a specific request from the clinical pharmacology team at the Agency, one study designated as a special population study, was conducted in the US at a dose of 25 µmol/kg. It included the determination of PK (serum, urine and feces) and PD (MRI signal intensity) in 9 groups of patients with following conditions: hepatic impairment (three groups, mild, moderate and severe hepatic impairment); renal impairment (two groups, moderate and end stage renal impairment); concurrent renal and hepatic impairment; non-elderly (<65 yr age) males and non-elderly females; and elderly (>65 yr age).

2.2.2 What is the basis for selecting the response endpoints, i.e, clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

For a diagnostic imaging agent, the pharmacodynamic variables based on measurements of the signal enhancement at the target site, are directly related to the presence of the contrast agent at the target site. The real time PD measurements obtained in the studies, therefore directly reflect the presence of Gd-EOB-DTPA in the liver. The pharmacodynamic dose response was investigated in two clinical pharmacology studies in volunteers to characterize the time course of signal enhancement in the liver at four dose levels (dose range of 10–100 µmol /kg) using two standard T1-weighted pulse sequences. MR signal enhancement was measured as a function of time after administration of Gd-EOB-DTPA. The % MR signal enhancement relative to pre-dose baseline values was the pharmacodynamic measure. The signal intensity increased in a dose dependent fashion from 10 µmol/kg to 50 µmol/kg. No increase was noted from 50 µmol/kg to 100 µmol/kg. The highest dose of the contrast agent produced susceptibility effects in liver during prolonged imaging phase and was therefore regarded as an overdose for imaging studies. Prolonged signal enhancement of the liver was present for more than 2 hours after administration of the contrast agent for all doses.

The European phase II studies were performed in a randomized, double-blind, dose-ranging fashion. The first phase II study tested 3 dose groups in a parallel group design, performing a pair comparison between the three doses. A different design was chosen for the second dose finding study in which four dose groups were tested against placebo to obtain a dose response.

The changes in diagnostic confidence regarding the primary indication (i.e. lesion type evaluated) when all relevant pre-and post-contrast MR images were compared, was chosen as the primary variable in all these studies. Diagnostic confidence was defined by the sponsor as a cumulative measure reflecting all relevant components together which contribute to the radiologist's assessment and which were assessed separately as secondary endpoints shown in the definition as used in the study protocols: (" the diagnostic confidence was to be based on the complete clinical picture for which the patient was referred to MRI and, in particular on the information available on MR scans regarding primary indication, including: number of lesions, lesion size, location of lesion(s) by liver segments visual evaluation of lesion(s), characterization of lesions, change in diagnosis.

With regard to efficacy the evaluation of the images was done without any knowledge of the respective doses and the blinding code was broken only after data entry had been completed and the database was locked. For the identification of the best imaging time point the evaluation of quantitative and objective technical parameters such as signal to noise (S/N) and contrast to noise (C/N) calculations based on signal intensity measurements provided additional reliable and sufficient data.

Based upon the results of these two studies the sponsor selected 25 μmol/kg dose for the Phase III clinical studies.

2.2.4 Exposure-response Evaluation

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Primovist is a contrast agent with specificity to hepatocytes. By that mechanism potential liver tumors are visualized in magnetic resonance

imaging. A PK study was conducted to study the differences in the signal intensity in the liver prior to and after the administration of 4 increasing doses of Primovist i.e. 10 μmol/kg, 25 μmol/kg, 50 μmol/kg, and 100 μmol/kg. The subjects were studied in a —— super conducting clinical MR imager. Two T1-weighted pulse sequences were used- spin echo sequence and gradient echo sequence. The imaging was performed for the first two hrs after the injection of contrast agent and again at 6 hrs post-injection and at 24 hr and 48 hrs in some subjects. The results showed that the contrast enhancement of the liver was homogenous at all dosages and at all time points.

The recommended dose of 25 μmol/kg gave a 50-55% increase in signal intensity in the lesion free portion of liver. A significant enhancement in signal intensity in liver was seen at 10 minute post-injection. Plateau enhancement is reached within 20 min post-injection. A further minimal increase was seen at 45 minutes.

2.2.4.2 What are characteristics of the exposure-response relationship (dose-response, concentration-response) for safety?

There are no apparent safety concerns with a dose of 25 μmol/kg of body weight except for NSF in severe renal impaired subjects for which "boxed warning" on primovist label.

2.2.4.3 Does this drug prolong QT or QTc interval?

Primovist does not prolong QT or QTc interval.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose selected by the sponsor based upon the S/N, C/N ratios and using confidence interval appeared scientifically sound and there are no unresolved dosing issues.

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the PK characteristics of the drug and its major metabolite?

The analysis of pharmacokinetic parameters was performed using a 2-compartment model in healthy Japanese male volunteers. At any dose, Gd was eliminated from plasma in a biphasic manner. The half-lives of Phase I and Phase II were 0.11 to 0.21 hr and 1.3 to 1.6 hr, respectively. The AUC increased dose-dependently, and there was a linear relationship between dose and AUC in the dose range from 25 to 100 μmol Gd/kg. No marked difference between the doses was observed in any other parameters.

Time-course profile of plasma concentrations Gd concentrations in plasma increased in proportion to dose, and the elimination from plasma was rapid. At any dose, the plasma Gd concentrations at 1 hr and 4 hr after injection decreased to about 1/10 and 1/50, respectively, of the concentration at 2 min after injection. The plasma Gd concentration under the detection limit was achieved at 12 hr after injection at a dose of 25 μmol Gd/kg and at 24 hr after injection at 50 and 100 μmol Gd/kg.

Fecal and urinary excretion at any dose, the urinary excretion of Gd was almost complete by the first 6 hr following administration. Urinary excretion for the first 4 days following administration was between 53.1% and 56.6% of the administered dose. On the other hand, the fecal excretion of Gd was incomplete even 4 days after administration at any dose, and the 4-day fecal excretion was between 32.1% and 39.3% of the administered dose. The total recovery of Gd excreted into feces and urine during the first 4 days following administration was between 86.5% and 95.9%. Subjects No. 13, 23 and 25 experienced delayed defecation, and the first defecation was 4 days after administration.

After bolus injection (dose, 10 – 100 μmol /kg BW) the rapid removal of Gd-EOB-DTPA from the circulation was attributed to a rapid renal elimination and simultaneous uptake by the liver. The AUC (0-4 h) accounted for about 90% of the AUC (0-infinity). Although the hepatic uptake and disposition of Gd-EOB-DTPA is known to be mediated by an active carrier, mean terminal half-life (range, 1.1 - 1.6 h), and total clearance (range, 224 - 272 mL/min) remained unchanged as well as the fecal and urinary excretion (50: 50 proportion) up to a 4-fold higher dose than the suggested clinical dose indicating that disposition processes are not saturated. Rapid and efficient urinary excretion and a dose independent renal

clearance at a dose 20-fold higher than the suggested clinical dose, were indicative of the governing role of renal elimination in the pharmacokinetics of Gd-EOB-DTPA.

2.2.5.4 What are the characteristics of drug metabolism?

The assays for biotransformation show that no significant metabolism or configurational change of Gd-EOB-DTPA in the blood of volunteers. The contrast agent is eliminated into urine in an unchanged fashion.

The analysis of the urine samples 6 h p.i. on a chiral HPLC column revealed no indication of a configurational change at the chiral center of Gd-EOB-DTPA. No conversion to the R-isomer was found.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (such as renal and hepatic dysfunction) influence pharmacokinetics (exposure)?

The sponsor studied the pharmacokinetics of primovist in several special population groups including mild, moderate, and severe hepatic impaired patients (Child-Pugh classification A-C). Another group of patients with moderate renal impairment, end stage renal disease (ESRD) patients, and moderate renal plus hepatic impairment was studied as well. The pharmacokinetic parameters derived from serum concentration data of Gd-EOB-DTPA were not markedly altered except in end stage renal failure (ESRF). Mild to severe hepatic impairment (Child-Pugh classification A-C, Groups 1-3) and moderate renal impairment (creatinine clearance as low as 30 mL/minute) did not markedly change the pharmacokinetic parameter values (e.g., compared to control, total clearance, CLt decreased by 19-41%, and terminal t-half increased by 14- 49%).

Pharmacokinetics of Gd-EOB-DTPA were markedly different in ESRF (e.g. CLt was only 17% of that in the control, terminal $t_{1/2}$ was about 12-fold higher than that in controls, and extent of fecal excretion was relatively higher). Fecal excretion of Gd-EOB-DTPA was markedly reduced (<0.5 % of dose) in the hepatic patients with high (>3 mg/dL) serum bilirubin levels, CLt and terminal t-half, however, was not consistently influenced by the high serum bilirubin levels. Urinary excretion (range, 72- 95%) was markedly higher in the hepatic patients with serum bilirubin >3 mg/dL. Pharmacokinetics in patients with moderate renal impairment, moderate

hepatic impairment, and concurrent moderate renal plus moderate hepatic impairment were similar. In the elderly (>65 yr) patients, CLt was 22% lower and terminal t-half was 43 % higher, compared to the non-elderly (<65 yr) patients. In the female patients, CLt was 22% lower compared to the male patients.

Gd-EOB-DTPA was dialyzable. About 30% of the dose was removed during a 3-hour dialysis session started at 1 hour after the dose.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

No effect of diet, smoking or herbal product was studied by the sponsor.

2.4.2. Drug-Drug-Interactions:

Is Primovist a substrate of CYP enzymes?

Gd-EOB-DTPA is not metabolized, therefore hepatic cytochrome P450 enzymes are not involved in its disposition. Metabolic or pharmacological interactions of Gd-EOB-DTPA, therefore, are considered unlikely. Considering the properties of Gd-EOB-DTPA and its very limited clinical use (i.e. single dose administration in a medical facility under qualified supervision) studies of pharmacokinetic drug-drug interactions of Gd-EOB-DTPA have not been undertaken.

2.2.4.2 Are there any metabolic/transporter pathways that may be important?

The results in laboratory animal models indicated that the organic anion transporting polypeptides (OATP) and energy dependent organic anion transporter (cMOAT) are involved in Gd-EOB-DTPA uptake into hepatocytes and subsequent excretion into the bile. It is possible that Gd-EOB-DTPA may compete with the known substrates (concomitant drugs and nutrients) of these transporters. Based on the following properties of Gd-

EOB-DTPA drug-drug interaction potential of Gd-EOB-DTPA is considered to be of no significant concern. Gd-EOB-DTPA is highly water soluble and a hydrophilic substance. Its clinical use involves a single dose application, it is rapidly excreted from the body (half-life of about 1.1 hour indicating rapid elimination from the circulation and return to near baseline MR-signal intensity of liver by 8 hours, indicating only a short duration of hepatic exposure).

The effect of pretreatment with several commonly used drugs on the hepatic signal enhancement was investigated in a study in laboratory rats. Consistent with known mechanism of its hepatic disposition, only rifampicin, a known potent inhibitor of OATP significantly inhibited the hepatic enhancement at doses 3-5 times the recommended clinical dose of rifampicin indicating that liver uptake of Gd-EOB-DTPA in humans may be inhibited by co-administration of rifampicin. It is therefore recommended that the patients administered primovist be not taking rifamycin and that sponsor conduct a phase IV study to understand the effect of OATP inhibitors on primovist uptake of liver.

2.5 General Biopharmaceutics

N/A

2.6 Analytical Section

Pharmacokinetic analysis was based on the concentration of gadolinium in serum, urine and feces as measured by Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES). Samples of the placebo group did not undergo pharmacokinetic analysis. Therefore, no quantitative gadolinium analysis was performed in the placebo group.

The assay validation of gadolinium concentration measurements in biological samples is described precisely in Research Report A749. In summary, the following procedure was performed:

Preparation of biological samples:

Serum and feces samples were digested to yield clear aqueous acidic solutions. Digestion was done by means of microwave irradiation [redacted] under strongly oxidizing conditions (presence of HNO_3 and H_2O_2) at high temperature (= 100 °C). Before digestion feces samples were freeze dried and homogenized and an aliquot of the freeze-dried feces powder was digested to yield clear aqueous solutions. Urine samples were only acidified to a final concentration of 20 % nitric acid und diluted if outside the specified measurement range.

Measurement of gadolinium concentration: The clear solutions obtained were not analyzed for the contrast agent itself but for the element gadolinium, the essential component of the contrast agent.

The gadolinium concentrations were determined by means of ICP-AES using commercially available equipment ([redacted]). Gadolinium was measured at a wavelength of 342.247 nm. The detection limit for Gd is about 0.06 pmol Gd/L but the lower limit of quantification is 0.1 pmol Gd/L. The range for quantitative measurement was between 0.1 and 500 pmol Gd/L. The measurements were performed in triplicate if possible. Before measurement the serum samples were digested and diluted six-fold. Consequently, in serum the lower limit of quantification was 0.6 pmol Gd/L.

Validation of measurements: Quality Control Samples (QCS) were prepared in urine and serum containing known amounts of Gd-EOB-DTPA. The QCS were treated in the same way as the biological test samples. Each day of analysis six QCS samples were included and accuracy and variation was calculated. Analysis was withdrawn in case either accuracy was < 90 % or > 110 % or variation of the measurement of the QCS was > 10%. During analysis all runs were within the limits.

22 Page(s) Withheld

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4.2 Individual Study Review

Report AM 36: PK in Healthy Volunteers

A total of 23 subjects were investigated in this trial. 6 volunteers in each dose group were administered SH L 569 B, and 2 volunteers (in the highest dose group only 1 volunteer) received physiological saline solution. Within each of the 3 independent dose groups (0.2, 0.35 and 0.5 mmol Gadolinium-EOB-DTPA/kg bw), the study was performed as a controlled, randomized, double-blind comparison. Blood samples for pharmacokinetic analyses were taken before and up to 120 h after administration. Urine and feces were collected quantitatively for a six day period after administration.

Pharmacokinetic Results

Pharmacokinetic analysis was based on the concentration of gadolinium in serum, urine and feces as measured by Inductively Coupled Plasma Atomic Emission Spectrometry. Samples of the placebo group did not undergo pharmacokinetic analysis.

Serum Concentration-Time Profile:

In the first three hours after infusion of the contrast medium the serum concentrations declined rapidly to about 7% of the highest concentrations recorded at the end of the 10-minute infusion. In the post 3-hour period the decline was slower and appeared log-linear for the low and medium dose group (0.2 and 0.35 mmol Gd-EOB-DTPA) whereas for the high dose group (0.5 mmol Gd-EOB-DTPA) the log-linear phase was apparent in the post 4-hour and post 6-hour period.

For the low dose group (0.2 mmol Gadolinium-EOB-DTPA/kg) quantifiable amounts of gadolinium in serum were observed up to 12 h p.i. for all volunteers. The same hold true for the medium dose group (0.35 mmol Gadolinium-EOB-DTPA/kg) with the exception of one volunteer who showed quantifiable amounts up to 24 h p.i. For the high dose group (0.5 mmol Gadolinium-EOB-DTPA/kg) four volunteers revealed measurable amounts up to 24 h p.i. and two volunteers up to 36 h p.i. The dose-normalized serum concentration-time curves were super-imposable for the low and medium doses (Figure 2); they were not super-imposable for the

high dose during the first three hours p.i. There were significant differences between the highest dose group and the two other dose groups in the dose-normalized AUC.

Serum:
Considering the begin of the ten-minute infusion period as time point 0 (t=0) about five mL of blood samples each were taken at the following time points: 0, 0.042, 0.083, 0.125, 0.167, 0.21, 0.25, 0.33, 0.5, 0.67, 0.92, 1.17, 1.67, 2.17, 3, 4, 6, 8, 12, 24, 36, 72 and 120 h after the begin of infusion. Blood without anticoagulant additions was allowed to clot at room temperature. Serum was separated by centrifugation, transferred to labeled containers and frozen at -20 °C until quantitative analysis for gadolinium concentration. PK profiles of primovist in healthy volunteers are shown in Table II.

Table II. PK Parameters for Primovist in healthy volunteers

µmol/kg Dose	Statistics	AUC/dose (0-inf) [µmol·h/L]	AUC/dose (0-t-last) [µmol·h/L]	AUC/dose (0-6h) [µmol·h/L]	excretion urine [%]	excretion feces [%]
0.2	N	6	6	6	6	6
	Mean	6155,00	6115,83	5846,67	43,60	36,78
	STD	400,78	414,73	418,70	8,58	8,53
	Min	5705,00	5650,00	5375	32,70	25,80
	Max	6695,00	6660,00	6350	51,30	46,40
	Median	6085,00	6052,50	5770,00	47,10	39,15
0.35	N	6	6	6	5	5
	Mean	6977,14	6900,48	6532,38	53,38	34,05
	STD	615,60	599,30	548,53	7,40	6,89
	Min	6180,00	6134,29	5891,43	36,80	25,70
	Max	7931,43	7845,71	7405,71	58,10	58,10
	Median	6904,29	6850,00	6492,86	55,20	39,10
0.50	N	6	6	6	6	6
	Mean	7887,00	7875,33	7310,00	59,05	27,10
	STD	584,22	586,00	595,64	5,60	8,08
	Min	6766,00	6750,00	6208,00	53,70	11,70
	Max	8628,00	8622,00	8228,00	68,10	34,10
	Median	7966,00	7949,00	7295,00	56,65	29,70

Urine:
Urine was collected quantitatively for a six day period with the following collection intervals: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120 and 320-144 h after application. The volume and the specific weight was measured. Specimen of the urine samples were frozen at -20 °C until quantitative analysis for gadolinium concentration.

Feces:
Feces was collected quantitatively for a six day period with a daily collection interval. The weight of each feces specimen was measured and the samples were frozen at - 20°C until quantitative analysis for gadolinium concentration.

Elimination
The gadolinium was excreted in urine and feces up to 6 hrs postinjection in both urine and feces. The mean (sd) values of renal excretion [% of dose] were 43.6 (8.6), 57.0 (1.4) and 59.1 (5.6) and the corresponding values for fecal excretion were 36.8 (8.5), 36.0 (7.3) and 27.1 (8.1) for the low, medium and high dose, respectively. The total recovery [% of dose] was between 60 and 100 with mean values of 80.4, 93.1 and 86.2 for the low, medium and high dose group, respectively.

With increasing dose levels the renally excreted fraction of dose increased ($p < 0.05$) whereas the fecally excreted fraction of dose slightly decreased as is demonstrated in Figure 3.

The mean (sd) values of renal excretion as expressed in percent of dose were 43.6 (8.6), 57.0 (1.4) and 59.1 (5.6) and the corresponding values for fecal excretion were 36.8 (8.5), 36.0 (7.3) and 27.1 (8.1) for the low, medium and high dose, respectively. The total recovery expressed in % of dose was between 60 and 100 with mean values of 80.4, 93.1 and 86.2 for the low, medium and high dose group, respectively (Figure 3). The urinary excretion rate was rapid and independent of dose. The half life calculated from urine data was about 2 h for all dose groups. The renal clearance of about 100 mL/min suggest glomerular filtration as the main pathway of renal excretion.

Conclusion

The results indicate some saturation in the hepatobiliary disposition of Gadolinium-EOB-DTPA especially for the highest dose tested, i.e. 0.5 mmol Gadolinium-EOB-DTPA/kg. However, renal excretion compensates saturation in hepatobiliary disposition of Gadolinium-EOB-DTPA.

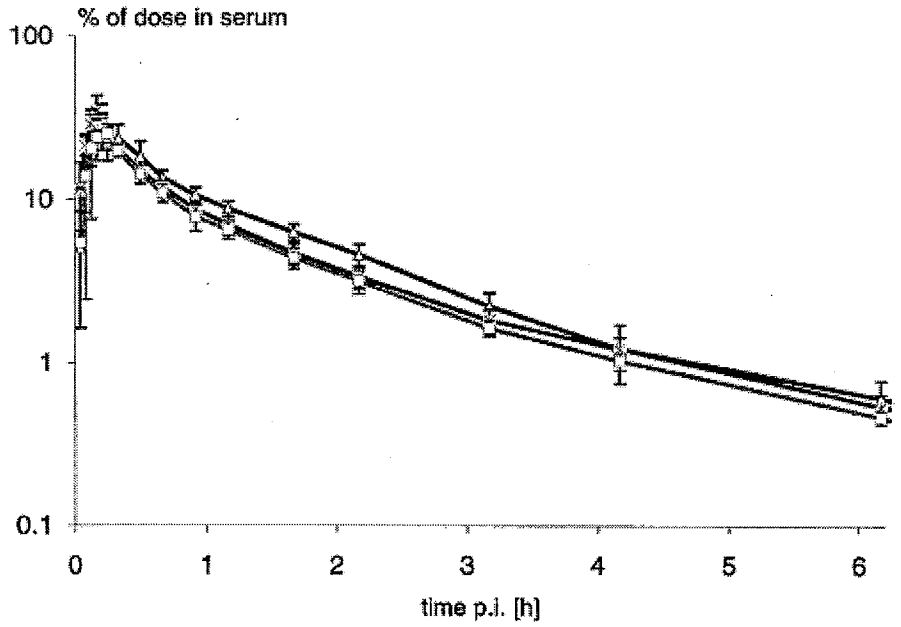

Figure 2. Serum concentrations of primovist for different dose groups (0.2, 0.35, and 0.5 mmol/kg)

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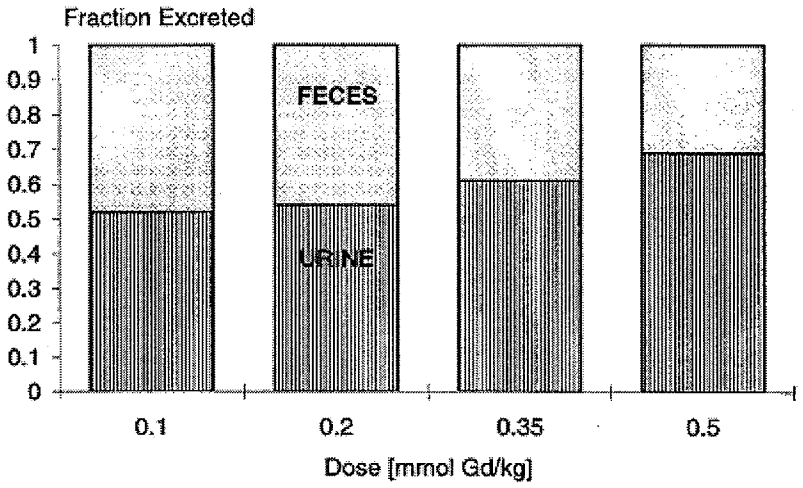

Figure 3. Excretion of primovist based upon dose

Quantitative gadolinium analysis

Pharmacokinetic analysis was based on the concentration of gadolinium in serum, urine and feces as measured by Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES). Samples of the placebo group did not undergo pharmacokinetic analysis. Therefore, no quantitative gadolinium analysis was performed in the placebo group.

The assay validation of gadolinium concentration measurements in biological samples is described precisely in Research Report A749. In summary, the following procedure was performed:

Preparation of biological samples:

Serum and feces samples were digested to yield clear aqueous acidic solutions. Digestion was done by means of microwave irradiation under strongly oxidizing conditions (presence of HNO_3 and H_2O_2) at high temperature (> 100 °C). Before digestion feces samples were freeze dried and homogenized and an aliquot of the freeze-dried feces powder was digested to yield clear aqueous solutions. Urine samples were only acidified to a final concentration of 20 % nitric acid und diluted if outside the specified measurement range.

Measurement of gadolinium concentration:

The clear solutions obtained were not analyzed for the contrast agent itself but for the element gadolinium, the essential component of the contrast agent.

The gadolinium concentrations were determined by means of ICP-AES (Inductively Coupled Plasma Atomic Emission Spectrometry) using commercially available equipment ( ). Gadolinium was measured at a wavelength of 342.247 nm. The detection limit for Gd is about 0.06 pmol Gd/L but the lower limit of quantification is 0.1 pmol Gd/L. The range for quantitative measurement was between 0.1 and 500 pmol Gd/L. The measurements were performed in triplicate if possible. Before measurement the serum samples were digested and diluted six-fold. Consequently, in serum the lower limit of quantification was 0.6 pmol Gd/L.

Validation of measurements:

Quality Control Samples (QCS) were prepared in urine and serum containing known amounts of Gd-EOB-DTPA. The QCS were treated in the same way as the biological test samples. Each day of analysis six QCS samples were included and accuracy and variation was calculated. Analysis was withdrawn in case either accuracy was < 90 % or > 110 % or variation of the measurement of the QCS was > 10%. During analysis all runs were within the limits.

STUDY A04410: Special Population PK

The objectives of this study were to determine the safety, pharmacokinetics, and pharmacodynamics (through MR imaging of the liver and related structures) of gadolinium-ethoxybenzyl-diethylene triaminepentaacetic acid (Gd-EOB-DTPA) in groups of volunteer patients with 1) various levels of impaired hepatic function, 2) impaired renal function, 3) coexistent hepatic and renal impairment, and 4) a control group of healthy volunteers matched for age, sex, weight, and smoking habits. A group of healthy elderly volunteers, and an aggregate group consisting of an equal number of healthy male and female volunteers were also included.

METHODOLOGY:

This was a single center, open-label, parallel-group study in which groups of patients with various levels of hepatic and/or renal impairment and healthy volunteers received a single intravenous bolus dose of Gd-EOB-DTPA (SH L569 B) under well controlled conditions. Assignment of patients to a specific group was based on the screening and baseline evaluations. Safety, pharmacokinetics, and pharmacodynamics were investigated and compared to results obtained in a healthy volunteer control group matched for age, sex, weight and smoking habits. Safety, pharmacokinetics and pharmacodynamics were also investigated in a group of elderly healthy volunteers and an equal number of healthy males and females. Pharmacodynamics were assessed through MR imaging of the liver and related structures. End stage renal failure patients, dosed on a dialysis day, did not undergo MR imaging for pharmacodynamics but permitted evaluation of the dialysance of the study drug.
The patients were divided into nine groups in this Study: Group 1: Mild Hepatic Impairment, Child-Pugh Class A; Group 2: Moderate Hepatic Impairment, Child-Pugh Class B; Group 3: Severe Hepatic Impairment, Child-Pugh Class C; Group 4: Moderate Renal Impairment, Creatinine Clearance 30-50 mL/minute; Group 5a: End Stage Renal Failure, requiring intermittent hemodialysis, dosed during interdialytic period Group 5b: End Stage Renal Failure, requiring intermittent hemodialysis, dosed 1 hour prior to hemodialysis; Group 6: Moderate Hepatic and Moderate Renal Impairment (patients had both conditions); Group 7: Control, Healthy Patients: demographic means matched to demographic means of patients in Groups 1-6 above ; Group 8: Healthy Patients, 3 males and 3 females, aged

65 or over; Group 9: Healthy Patients, 6 males and 6 females when combined with Group 7, under the age of 65.

PK/PD:

Blood samples for determination of serum concentration of gadolinium were obtained at pre-dose, at 3, 6, 9, 15, 30 and 45 minutes, and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96 and 120 hours after the dose. Urine samples for determination of Gd-EOB-DTPA were obtained at the following times: 1 hour prior to dosing and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120 and 120-144 hours post-dose. Total feces excreted over the 6 days after the dose of Gd-EOB-DTPA were collected quantitatively. The patients were encouraged to provide feces samples at the following nominal intervals: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 hours. The following pharmacokinetic variables were estimated: area under the curve (AUC), terminal-t-half (t1/2), total serum clearance (CLt), renal clearance (CLr), non-renal clearance (CLnr), volume of distribution at steady-state (Vss), mean residence time (MRT) and effective-t-half (eff t1/2). Amount of Gd-EOB-DTPA excreted in each urine and feces collection interval and the cumulative excretion was calculated in terms of percent of administered dose. Hemodialysis clearance (CLdial) was calculated (Group 5b only).

MR signal intensity (SI) in designated and constant regions of interest (ROI) in the liver were used (averaged) as the pharmacodynamic determinant of Gd-EOB-DTPA as a function of time post-dose. Imaging was performed immediately before dose of Gd-EOB-DTPA (baseline pre-study drug MRI).

Post-administration of study drug, MR imaging was performed continuously for the first 2 minutes (4 sequences, at 30-second intervals), at 5 minutes, then every 5 minutes to 30 minutes, at 45 minutes, at 60 minutes, at 4 hours, at 6 hours, and at 8 hours post-dose. Imaging was performed at 24 hours and every 24 hours thereafter, only if the SI of the ROI #1 in the liver, at the prior time point, remained 20% or more above the pre-dose (baseline) SI. SI was determined in the chosen intrahepatic ROIs. SI was also determined for the vascular structures (aorta, portal vein, intrahepatic inferior vena cava), the extrahepatic common bile duct and the paraspinal muscle to assess the patient's specific hemodynamics. All were standardized against the external phantom (external standard) and the paraspinal muscle (internal standard). An additional analysis was performed using 3 liver ROIs pooled

and averaged (the primary one and two supplemental ones), normalized to both standards.

The following pharmacodynamic variables were evaluated: time to maximum SI, in every ROI; duration of plateau SI in liver ROI (plateau defined as peak SI ± 20%); area under SI-t curve by trapezoidal rule; time to return to within 20% of baseline SI in the liver ROI.

PK RESULTS:

Peak serum concentration was similar in all study groups (Table III, IV and V). The pharmacokinetic parameters derived from serum concentration data of Gd-EOB-DTPA were not markedly altered except in end stage renal failure (ESRF). Mild to severe hepatic impairment (Child-Pugh classification A-C, Groups 1-3) and moderate renal impairment (creatinine clearance as low as 30 mL/minute, Group 4) did not markedly change the pharmacokinetic parameter values (e.g., compared to control [Group 7], total clearance, CLt decreased by 19-41%, and terminal t-half increased by 14-49%). Pharmacokinetics of Gd-EOB-DTPA were markedly different in ESRF (e.g. CLt was only 17% of that in the control [Group 7], terminal t-half was about 12-fold higher than that in Group 7, and extent of fecal excretion was relatively higher). Large inter- and intra-group variability was observed in the urinary and fecal excretion results, which were considered non-representative for quantitative interpretations due to suspected irregularities in the sample collection and handling. Fecal excretion of Gd-EOB-DTPA was markedly reduced (<0.5 % of dose) in the hepatic patients with high (>3 mg/dL) serum bilirubin levels, CLt and terminal t-half, however, was not consistently influenced by the high serum bilirubin levels. Urinary excretion (range, 72- 95%) was markedly higher in the hepatic patients with serum bilirubin >3 mg/dL. Pharmacokinetics in patients with moderate renal impairment, moderate hepatic impairment, and concurrent moderate renal plus moderate hepatic impairment were similar. In the elderly (>65 yr) patients, CLt was 22% lower and terminal t-half was 43 % higher, compared to the non-elderly (<65 yr) patients. In the female patients, CLt was 22% lower compared to the male patients.

Gd-EOB-DTPA was dialyzable. About 30% of the dose was removed during a 3-hour dialysis session started at 1 hour after the dose.

Table III. Effect of Hepatic Impairment on PK of primovist

Parameter	Group Mean				K-W p-value
	G 1 C-P A	G 2 C-P B	G 3 C-P C	G 7 Control	
Cmax	210	202	174	195	0.732
AUC (0-inf)	252	210	259	160	0.016
CL total	122	170	140	209	0.015
CL renal	72.8	97.3	90.9	101	0.356
Terminal-t-half	2.01	1.88	2.62	1.76	0.128
Effective-t-half	1.58	1.49	1.95	1.15	0.021
MRT	2.28	2.16	2.82	1.67	0.020
Vss	16.9	19.3	20.1	19.5	0.446
Urinary Excr.	64.5	56.2	61.3	48.4	0.596
Fecal Excr.	20.7	20.7	5.74	31.3	0.057
Total Excr.	85.3	76.9	67.2	79.7	0.403

Table IV. Effect of Renal Impairment on PK of primovist

Parameter	Group Mean			K-W p-value
	G 4 Moderate	G 5a ESRF	G 7 Normal	
Cmax	170	161	195	0.562
AUC (0-inf)	237	903	160	0.004
CL total	150	36.0	209	0.006
CL renal	69.6	-	101	0.149
Terminal-t-half	2.15	20.4	1.76	0.014
Effective-t-half	1.66	11.9	1.15	0.005
MRT	2.39	17.2	1.67	0.005
Vss	18.2	36.9	19.5	0.028
Urinary Excr.	43.6	-	48.4	0.522
Fecal Excr.	39.4	54.9	31.3	0.404
Total Excr.	83.1	54.9	79.7	0.183

Table V. Effect of hepatic and renal impairment on PK of primovist

Parameter	G 2 Mod Hep	G 4 Mod Renal	G 6 Mod Hep & Mod Renal	p-value
Cmax	201.50	169.50	172.00	0.610
AUC (0-inf)	209.50	236.50	244.50	0.711
CL total	169.50	150.33	165.00	0.832
CL renal	97.35	69.59	81.23	0.511
Terminal-t-half	1.88	2.15	2.75	0.135
Effective-t-half	1.49	1.66	1.67	0.863
MRT	2.16	2.39	2.41	0.863
Vss	19.30	18.17	19.40	0.993
Urinary Excr.	56.18	43.63	53.75	0.277
Fecal Excr.	20.73	39.47	25.20	0.112
Total Excr.	76.92	83.08	78.98	0.745

PK Conclusion for special population:

Out of all the special population variables investigated (hepatic impairment, renal impairment, end stage renal failure, coexistent renal and hepatic impairment, gender and age) only the end stage renal failure (ESRF) had the most remarkable influence on the pharmacokinetics of Gd- EOB-DTPA. In the ESRF the terminal half-life was remarkably longer (20.4 h compared to < 3 h in all other groups studied) and the systemic exposure was higher (AUC was 5.6-fold higher in ESRF compared to the control group) (Table I). Primovist is a structurally similar analog of magnevist. The basic chelating entity for primovist is the same (DTPA) as magnevist. We know that there are at least 15 cases of nephrogenic systemic fibrosis (NSF) reported in the AERS for magnevist. The current scientific understanding is that there is de-complexation of free Gd+3 ions from the chelate that gives rise to NSF. It is therefore, recommended that use of primovist —

——— in patients with ESRF and in patients with GFR <30 ml/min.

PD RESULTS:

MR Signal Intensity (SI) in a designated and constant ROI of about 1 cm or more in diameter was selected within the liver parenchyma (ROI #1) and was used as the pharmacodynamic determinant of Gd-EOB-DTPA as a function of time post-dose. The ROI was in a homogeneous region of the liver, avoiding any vessels or space-occupying structures; the mean SI was recorded along with the minimum, maximum, SD and area measured. The

"slice" selected for this measure was that representing the most intense homogeneous enhancement of the liver parenchyma at the first time point when this occurred. This "slice" remained as constant as possible throughout all imaging time points. In order to insure representative measures of liver parenchymal enhancement, two additional ROIs were selected within the same slice, using the same criteria. The combined signal intensities of ROIs 1, 2 and 3 were averaged, yielding a single "average" value, the value used in all graphic displays and discussions.

A calibrating external standard (Magnevist® 0.25 mmol/L) was utilized to insure accurate quantitation of this SI measure. The paraspinal muscle was also independently used for standardization of measures. Results were expressed in SI numbers, after correction against the standard (normalized SI), and were correlated with the SI over related anatomic structures. Percent enhancement over baseline was used for profiling each group.

Liver parenchymal enhancement occurred in all groups, at a fixed uniform dose of 25 μmol/kg.

Maximal enhancement occurred in the "normal" Groups 7, 8 and 9. Enhancement was comparable in magnitude between them, as well as to Group 1 (mild hepatic impairment) and Group 4 (moderate renal impairment). Enhancement decreased with increasing severity of liver disease, as well as with coexistent liver and renal disease, Group 6. Enhancement was comparable between males and females, between patients under 65 years of age, and over 65 years of age.

The time to maximal parenchymal enhancement following study drug administration was comparable in all groups.

The area under the curve (AUC), an integration of enhancement over time, decreased inversely with increasing severity of liver disease, but was not affected significantly by the presence of moderate renal disease or coexistent liver and kidney disease, when normalized to phantom. When normalized to muscle, coexistent liver and kidney disease was associated with a reduction in AUC, comparable to that in patients with severe liver disease. Group 5a patients, on chronic hemodialysis, showed apparent decreased enhancement due, in part, to the relatively high iron content of the liver parenchyma, correlated with high serum ferritin levels.

Elevated bilirubin levels were associated with decreased maximal enhancement and reduced duration of enhancement, correlated with the hepatocyte transport system shared by bilirubin and Gd-EOB-DTPA.

Hemodynamic correlations between the various disease groups and the control group failed to reveal any consistent pattern. Large inter- and intragroup variability was observed.

STUDY A336

Tolerability and pharmacokinetics after intravenous administration of ZK 139834 (Gd-EOB-DTPA I SH L 569 8) in comparison with placebo treatment (first use in humans).

The objectives of this first phase I trial were to investigate the safety, tolerability and dose proportionality of kinetics and biotransformation of ZK 139 834 (Gd-EOB-DTPA / SH L 569 B) after single intravenous administration in young healthy male volunteers.

The new magnetic resonance liver imaging contrast agent was studied in a total of 44 healthy young male volunteers and compared with placebo. Four independent groups received increasing doses of SH L 569 B (10, 25, 50 and 100 µmol Gd/kg body weight (BW) by intravenous injection. Eight volunteers per dose group were treated with the test article and three with the same volume of 0.9% saline solution as placebo on a randomized double-blind basis.

Trial Design:

The trial was set up as a double blind, randomized (within dose levels) study comparing five treatments assigned to independent groups of volunteers.

According to the principle of dose titration, at each of four dose levels n = 11 volunteers were investigated; n = 8 volunteers were randomly assigned to the test compound and n = 3 volunteers were randomized to placebo treatment. At each dose level two blocks consisting of 5 or 6 volunteers, respectively, were considered at intervals of seven days.

The duration of treatment was one day, the duration of intensive observation was 5 days: the day prior to treatment (day -1), the treatment day (day 0) and three days following treatment (day 1 - 3). After medical evaluation of the results (days 0 - 4) of the previous dosage, the next higher dosage level was administered according to the same schedule in an interval of one week after the end of the second block.

A total of 52 parameters were analyzed for the assessment of the hematology, clinical chemistry and clotting status. Forty-five other parameters of urine were monitored over an observation period of 4 days. In addition to studies of hemodynamics (heart-rate, blood pressure and ECG), the volunteers were questioned openly about their complaints at specific time points before and after substance administration.

The pharmacokinetics of Gd-EOB-DTPA were investigated in all four dose groups (10, 25, 50, 100 µ mol Gd/kg). The serum, urine, and feces were collected over respectively 48-, 96- and 96- hour period after drug administration. The biological samples were analyzed for the element gadolinium, the essential component of the contrast agent, using a validated ICP-AES method (Inductively Coupled Plasma Atomic Emission Spectrometry). Pharmacokinetic analysis of serum gadolinium concentrations versus time and urinary excretion data were performed using compartment model independent and using an open two compartment model. The excretion of Gd-EOB-DTPA into urine and into feces was reported as the cumulative percentage of the injected dose up to the respective time point. Urinary excretion data was also evaluated using urinary excretion rate versus midpoint time.

Selected serum and urine samples were subjected to HPLC (High Pressure Liquid Chromatography) to investigate potential biotransformation (reversed phase HPLC) and to test integrity of the chiral center (chiral HPLC column). Element-specific detection by ICP-AES was used in connection with conventional photometric UV-detection.

PK Results:

In the first two hours serum concentrations declined rapidly to about 15% of the highest concentrations recorded at 2 minutes after the intravenous injection. In the post 2-hour period the decline was slower and appeared log-linear. Although the serum concentrations were measurable for up to 8 to 12

hours in the 50 and 100 pmol/kg dose groups, the AUC (0-4 h) accounted for about 90% of the AUC (0-). Urinary and fecal excretion over the 4-day collection period accounted for about equal portions of the administered dose (table VI). The urinary excretion was rapid; about 75%, 90%, 95%, and 99% of the total urinary excretion occured in respectively 0-2 h, 0-4 h, 0-6 h, and 0-12 h. The key pharmacokinetic and disposition parameters are listed in Table VI and Table VII.

Table VI. Pharmacokinetic parameters of Gd-EOB-DTPA evaluated in healthy volunteers after single intravenous administration of 10, 25, 50 and 100 pmol/kg.

Parameter	10 µmol/kg		25 µmol/kg		50 µmol/kg		100 µmol/kg	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cmax µmol/L	101	11.8	259	76.3	478	118	883	356
AUC(0-inf) µmol*h/L	48.3	6.4	142	20.7	300	49.2	569	75.4
Effective T1/2 (h)	0.93	0.07	0.96	0.07	0,99	0.10	1.04	0.10

Table VII. Pharmacokinetic parameters of Gd-EOB-DTPA evaluated in healthy volunteers after single intravenous administration of 10, 25, 50 and 100 pmol/kg.

Parameter	10 µmol/kg		25 µmol/kg		50 µmol/kg		100 µmol/kg	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total Serum Clearance mL/min	304	41.5	253	29.2	241	42.0	236	35.6
Renal Clearance mL/min	124	12.5	118	14.7	109	19.1	119	21.3
Urinary Excretion % dose	43.1	3.1	49.3	8.0	47.7	3.8	53.2	4.8
Fecal excretion %dose	51.2	9.2	41.6	13.1	46.6	4.0	48.2	4.7

Biotransformation assay

The HPLC analysis of 0-2 h and 4-6 h urine and 0.5 h serum samples from the higher dose groups (50 and 100 µmol/kg) indicated absence of significant metabolism of Gd-EOB-DTPA.

The analysis of the urine samples 6 h p.i. on a chiral HPLC column revealed no indication of a configurational change at the chiral center of Gd-EOB-DTPA. No conversion to the R-isomer was found.

CONCLUSIONS:

The pharmcokinetic results suggested dose linear pharmacokinetics of Gd-EOB-DTPA up to 100 pmol/kg. Thus, unlike in laboratory animal models, hepatocellular uptake in humans was not saturable in the dose range investigated in this study. Additionally, SH L 569 B was shown to have complete elimination from the body via urine and feces in about equal parts. The renal clearance of Gd-EOB-DTPA (109-124 mL/min) was virtually identical to the known glomerular filtration rate in humans (120 mL/min) suggesting absence of tubular secretion or reabsorption in the renal elimination process. From the pharmacokinetic point of view, Gd-EOB-DTPA posesses optimal properties to be a contrast agent for MRI especially for the liver.

The assays for biotransformation show that no significant metabolization or configurational change of Gd-EOB-DTPA occur in the blood of volunteers. The contrast agent Gd-EOB-DTPA is eliminated into urine in an unchanged fashion.

Results of the safety pharmacology and tolerability of the first phase I study demonstrate that Gd-EOB-DTPA in 0.25 molar concentration was well tolerated up to a dose of 100 µmol Gd/kg BW.

Methods Validation:

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1 Trade Secret / Confidential

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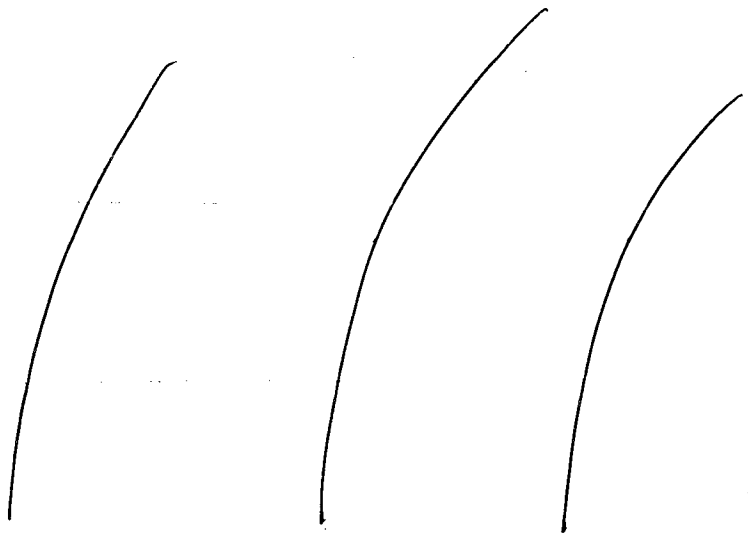


Dose Selection: Studies A337 and A04410:

For a diagnostic imaging agent, the pharmacodynamic variables based on measurements of the signal enhancement at the target site, are directly related to the presence of the contrast agent at the target site. The real time PD measurements obtained in the studies, therefore directly reflect the presence of Gd-EOB-DTPA in the liver. The pharmacodynamic dose response was investigated in two clinical pharmacology studies (Reports 5.3.4.2 A04410 and 5.3.4.1 A337) in volunteers to characterize the time course of signal enhancement in the liver at four dose levels (dose range of 10–100 µmol /kg) using two standard T1-weighted pulse sequences. MR signal enhancement was measured as a function of time after administration of Gd-EOB-DTPA. The % MR signal enhancement relative to pre-dose baseline values was the pharmacodynamic measure. The signal intensity increased in a dose dependent fashion from 10 µmol/kg to 50 µmol/kg. No increase was noted from 50 µmol/kg to 100 µmol/kg. The highest dose of the contrast agent produced susceptibility effects in liver during prolonged imaging phase and was therefore regarded as an overdose for imaging studies. Prolonged signal enhancement of the liver was present for more than 2 hours after administration of the contrast agent for all doses.

ZK 139834 is a contrast medium with specifity to hepatocytes. By that mechanism potential liver tumors are visualized in magnetic resonance imaging (MRI). Furthermore the elimination of ZK 139834 through the gall bladder affords the opportunity to visualize the biliary system.

The aim of the trial was to demonstrate the difference of the signal intensity in the liver prior to and after administration of 4 increasing doses of ZK 139834 as 0.25 molar solution ZK 139834. Information regarding the local and general tolerability in humans were also obtained.

Method:

A total of 16 healthy volunteers, age between 25 and 39 years, took part in this trial. Four volunteers each received 0.01, 0.025, 0.05, and 0.1 mmol ZK 139834/kg bodyweight in an open design. The contrast agent was administered at a rate of 2 mL/sec.

Safety and laboratory tests (33 parameters of hematology, clinical chemistry, and clotting status as well as 9 urinary parameters) were performed at baseline 2 days before and 24 hours after administration of the contrast agents. The volunteers were instructed to report immediately any adverse events and additionally questioned in an open manner at specific time points.

The volunteers were examined with a — superconducting clinical imager —————— using an identical imaging protocol. Imaging was performed before and then frequently for the first 2 hours after application of ZK 139834 and again 6 hours afterwards. Some volunteers of the 0.05 and 0.1 mmol ZK 139834/kg dose group were investigated by MR-imaging 24 h and also 48 h p.a. MR imaging of the upper abdomen was performed in the transaxial plane (8-mm section thickness, 4-mm section gap). Two T1- weighted pulse sequences were used for imaging before and after contrast application: spin- echo (SE) sequence and heavily T1-weighted gradient-echo (GRE) sequence with 256 frequency-encoding points for both sequences. The field of view was 40 x 40 cm. Radiofrequency transmit and receive attenuations were set for the preinjection images and were not changed for the postinjection images. Each volunteer was to be imaged together with a standard tube filled with an aqueous 0.5 mmol Gadopentetic acid dimeglumine solution. Signal intensity values for all organs and the standard were obtained by means of an

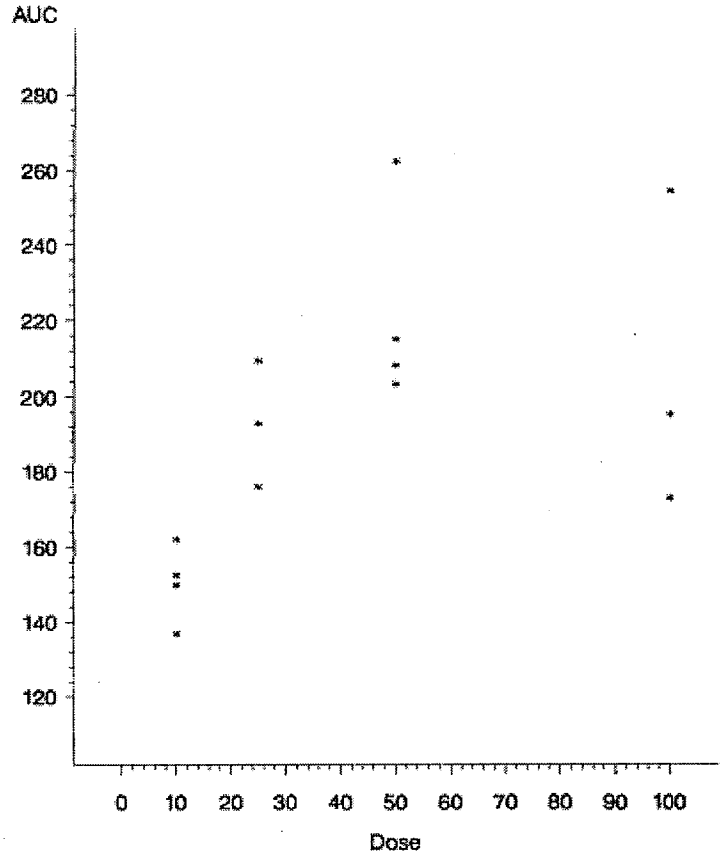
operator- defined region-of-interest for each pulse sequence and each time point.

Results:

ZK 139834 was well tolerated. The laboratory parameters did not reveal any clinically relevant changes attributable to ZK 139834. The hemodynamic and ECG parameters were not affected by increasing doses of the contrast agent and no adverse events occurred.

The contrast enhancement of the liver was homogeneous at all dosages and at all time points. For the doses 0.01, 0.025 and 0.05 mmol ZK 139834/kg a statistically significant dose dependency was observed with respect to the signal intensity of the liver on both pulse sequences. Comparison of the contrast enhancement produced by the different doses of ZK 139834 revealed a clinically significant difference between the dose of 0.025 mmol ZK 139834 /kg and 0.01 mmol ZK 139834/kg and a further increase of signal intensity at the dose 0.05 mmol ZK 139834/kg. The highest dose of the contrast agent produced susceptibility effects in the liver during the prolonged imaging phase and must therefore be regarded as an overdose for imaging studies. Prolonged signal enhancement of the liver was present for more than 2 h after administration of the contrast agent at all doses.

Figure 7. AUC (Area under curve) for liver with respect to time



The upper abdominal organs differed in their contrast enhancement after application of ZK 139834, only the organs statistically evaluated (liver, spleen and inferior vena cava) were considered in this report.

The spleen showed contrast enhancement only during the first minutes after application of the contrast agent with a maximum between the 1st and 3rd min and a subsequent decrease in signal intensity for most of the volunteers. The course of the contrast enhancement of this organ was similar to that of the inferior vena cava; although higher values in signal intensity were observed.

The liver likewise showed early enhancement with a steep increase in signal intensity during the first 2 minutes and a further, though slower, increase up to about the 20th to 30th min, followed by a plateau-like course until about 120 min after application of the contrast agent at dose 0.01, 0.025 and 0.05

mmol ZK 139834/kg. At the highest dose (0.1 mmol ZK 139834/kg), all volunteers showed a transient signal loss followed by a renewed increase, which has to be regarded as a susceptibility effect (standard as reference). The maximal signal intensity of this dose level did not reach the maximum value of the 0.05 mmol ZK 139834/kg dose.

The contrast enhancement was markedly reduced after 6 hours and almost reached the baseline signal intensity for the two lower doses, while there was still a residual enhancement on the T1-weighted GRE images of 1.59 and 1.69, on the spin-echo sequences of 1.52 and 2.02 for the doses of 0.05 mmol and 0.1 mmol ZK 139834/kg, respectively (mean values), standard as reference, similar or a little lower values were obtained with muscle as reference.

For the dose of 0.05 mmol ZK 139834/kg the contrast enhancement completely reached the baseline signal intensity after 24 h. For the higher dose of 0.1 mmol ZK 139834/kg the effect had almost returned to baseline after 24 h, but completely after 48 h (on both pulse sequences, muscle as reference).

The contrast enhancement of the liver was homogeneous at all dosages and at all time points.

Target variables

To get interpretable data the signal in the liver was to be related to a reference. The standard tube was measured for this reason. Since their was pretty much variation of the standard signal intensity in time the signal intensity of the muscle was used as a further reference. Both, the signal intensity of the liver and of the reference were related to their baseline values before they were related to each other. Statistical and systemical noise which were observed at each time point were not considered within transformations.

Thus, the following primary variables were considered: The relative signal intensity (RSI) of the liver normalized by the signal of the standard

$$\frac{SIliver(t) - SI\ liver(0)\ \text{(calculated for each time point t).}}{SIstandard(t) - SIstandard\ (0)}$$

The relative signal intensity (RSI) of the liver normalized by the signal of the muscle

$$\frac{SIliver(t) - SIliver(0) \text{ calculated for each time point t}}{SImuscle(t) - SImuscle(0)}$$

Figure 8. AUC (liver) for various doses using gradient echo sequence

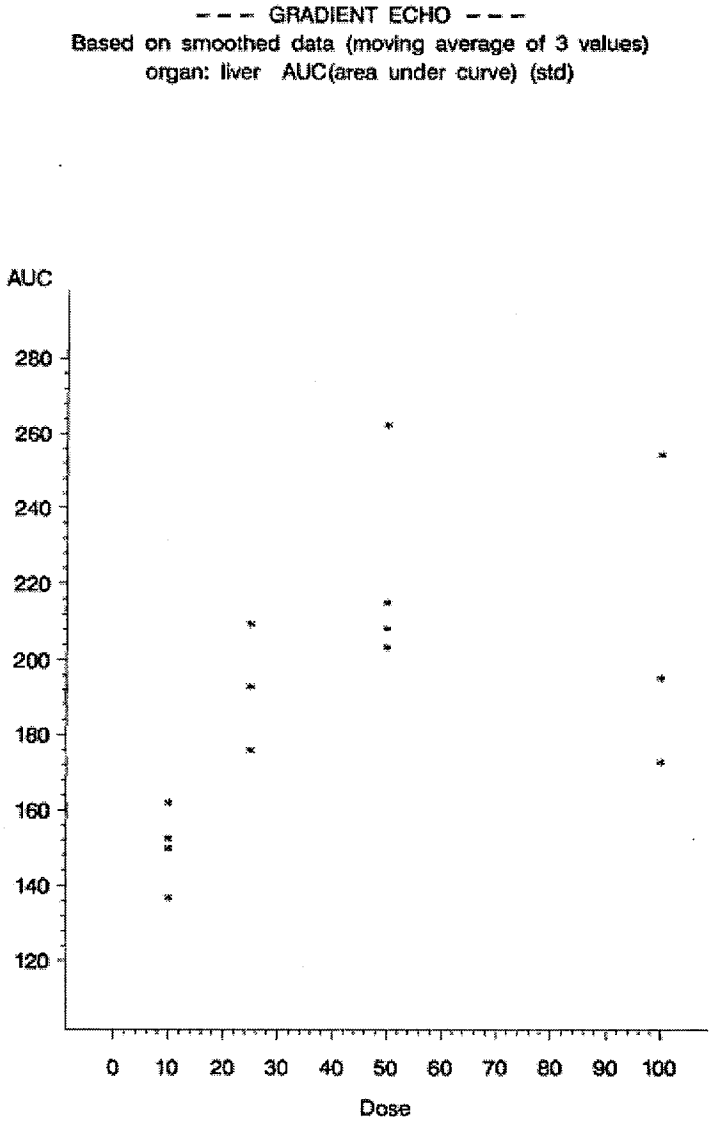
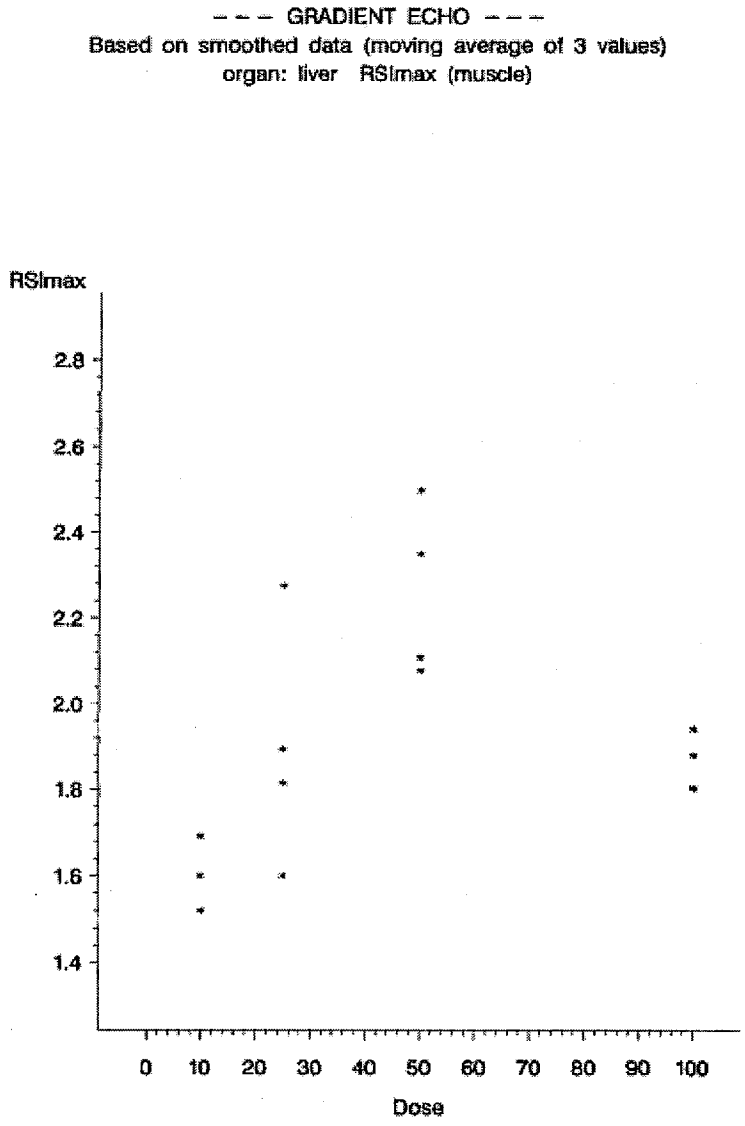


Figure 9. Relative signal intensity (RSI) of liver normalized by the signal of the muscle using gradient echo MR.



Evaluation of GRE-data based on standard as reference

For the liver a continuous increase of normalized signal intensity was observed during the first 10 minutes after application of the trial substance. Median values higher than 1.4 were reached first after 16 minutes and occured until 90 minutes after application. The maximum median value of 1.50 was observed after 75 minutes but there was almost no difference in signal within the time interval 16 to 90 minutes.

After 360 minutes the original values of liver signal intensity had almost returned to baseline values, the mean was 1.16, the median value 1.14, the maximum value was 1.39.

AUC-values for the smoothed curves of the liver signal (0 to 105 minutes) ranged between 136.8 and 162.0. The median value was 151.2 and the mean 150.3. The maximum relative signal intensities per volunteer ranged between 1.43 and 1.64, median 1.50 and mean value 1.52.

Evaluation of GRE-data based on muscle as reference

Similar results were seen for the liver when muscle data were used as reference. 10 minutes after application a median value of 1.4 was observed first. After 90 minutes the median value was still greater than 1.4 but had already decreased as compared to the maximum median of 1.53 that occurred 27 minutes after application. Inter-individual differences were small but volunteer no. 1 showed a little higher signal intensities as compared to the others 21, 27 and 33 minutes after application of the trial substance. After 360 minutes the original values of liver signal intensity had almost returned to baseline values, the mean and the median value were 1.15, the maximum value was 1.35.

AUC-values for the smoothed curves of the liver signal (0 to 105 minutes) ranged between 139.0 and 163.7. The median value was 153.5 and the mean 152.4. The maximum relative signal intensities per volunteer ranged between 3.36 and 1.69, median 1.56 and mean value 1.54.

Evaluation of SE-data based on muscle as reference

Comparable results were observed for the signal intensity of the liver when muscle data were used as reference. Again the normalized data were higher as compared to those that resulted with standard as reference. This was true for mean and maximum values but not for median values. The maximum median value of 1.67 was observed 34 minutes after application. Signal intensities amounted at least 1.6 in the interval between 17 and 61 minutes. After 360 minutes the original values of liver signal intensity had almost returned to baseline values, the mean was 1.13, the median value 1.11, the maximum value was 1.34. AUC-values for the smoothed curves of the liver signal (0 to 105 minutes) ranged between 160.2 and 206.9. The median

value was 163.7 and the mean 173.6. The maximum relative signal intensities per volunteer ranged between 1.65 and 2.39, median 1.67 and mean value 1.84.

Results for the dose 0.025 mmol ZK 139834/kg BW

Gradient echo sequences:

Data were available until 360 minutes after application of the trial substance.

Evaluation of GRE-data based on standard as reference: For the liver a continuous increase of normalized signal intensity was observed during the first 45 minutes after application of the trial substance. Median values higher than 1.6 were reached already after six minutes, values higher than 1.8 after 27 minutes. These high values were observed until the end of the second hour after application. The maximum median value of 1.92 was observed after 45 minutes but there was almost no difference in signal within the time interval 27 to 105 minutes.

Conclusion:

ZK 139834 was well tolerated. The laboratory parameters did not reveal any clinically relevant changes attributable to ZK 139834. The hemodynamic and ECG parameters were not affected by increasing doses of the contrast agent and no adverse events occurred.

The contrast enhancement of the liver was homogeneous at all dosages and at all time points. For the doses 0.01, 0.025 and 0.05 mmol ZK 139834/kg a statistically significant dose dependency was observed with respect to the signal intensity of the liver on both pulse sequences. Comparison of the contrast enhancement produced by the different doses of ZK 139834 revealed a clinically significant difference between the dose of 0.025 mmol ZK 139834 /kg and 0.01 mmol ZK 139834/kg and a further increase of signal intensity at the dose 0.05 mmol ZK 139834/kg. The highest dose of the contrast agent produced susceptibility effects in the liver during the prolonged imaging phase and must therefore be regarded as an overdose for imaging studies. Prolonged signal enhancement of the liver was present for more than 2 h after administration of the contrast agent at all doses.

Dose Justification: European Study

Methodology:

The European phase II studies were performed in a randomized, double-blind, dose-ranging fashion. The first phase II study (5.3.5.1 AH 34) tested 3 dose groups in a parallel group design, performing a pair comparison between the three doses. A different design was chosen for the second dose finding study (5.3.5.1 AI 94) in which four dose groups were tested against placebo to obtain a dose response.

In both phase II studies, efficacy was evaluated by qualitative and quantitative parameters. The change in diagnostic confidence regarding the primary indication (i.e. lesion type evaluated) when all relevant pre-and post-contrast MR images were compared, was chosen as the primary variable in all these studies.

A few design elements of the phase 2 studies were identified which require a brief and critical discussion, such as:
- The use of diagnostic confidence as the primary endpoint;
- The standard of truth;
- The blinding.

Diagnostic confidence

Diagnostic confidence is a cumulative measure reflecting all relevant components together contribute to the radiologist's assessment and which were assessed separately as secondary endpoints shown in the definition as used in the study protocols: ("the diagnostic confidence was to be based on the complete clinical picture for which the patient was referred to MRI and, in particular on the information available on MR scans regarding primary indication, including:

number of lesions, lesion size, location of lesion(s) by liver segments visual evaluation of lesion(s), characterization of lesions, change in diagnosis.

Additional and/or more detailed information or the strengthening of the impression about one of the above mentioned parameters is bound to improve the diagnostic confidence.")

The definition shows that another important component is highlighted by the protocol definition. This is that "the strengthening of the impression of one of the above mentioned parameters is bound to improve the diagnostic confidence." This statement recognizes the most frequently occurring clinical setting or diagnostic question, which is that patients are referred to an imaging procedure such as MRI, because of a suspicion based on either clinical or other imaging information. The expected outcome of the MRI is either confirmation of this suspicion or its disproof. Thus, especially in the setting of confirmation of a suspicion, change in confidence may occur frequently without a concurrent change in more objective endpoints.

It is well-acknowledged that diagnostic confidence is a subjective parameter. However, in clinical situations it is relevant as it conceptualizes the diagnostic thinking efficacy, and links the technical and diagnostic efficacy of a contrast agent with the therapeutic management of the patient. For this reason, it is considered to be a reliable primary endpoint to determine the minimal effective, but robust dose for Gd-EOB-DTPA with regard to its intended clinical use to detect and to radiologically characterize liver lesions.

Standard of truth

The European phase II studies assessed several endpoints which were either technical (SI measurements) or subjective in nature, including diagnostic confidence as primary endpoint or change in visualization, border delineation etc. They did not require a direct comparison to the final diagnosis which could have been used as the standard of truth. However, for the endpoints evaluated in these studies (which play a more dominant role in dose comparative studies than in the confirmatory phase III studies), the lack of a truth standard is less critical and may be even not useful.

Blinding

The phase II studies were intended to provide information about the safety, the relative diagnostic performance of different dose groups and to identify the best imaging time point for Gd-EOB-DTPA. Both European phase II studies were double-blind. This is considered to be the superior and most appropriate design for the assessment of safety of the various dose groups.

With regard to efficacy the evaluation of the images was done without any knowledge of the respective doses and the blinding code was broken only after data entry had been completed and the database was locked. For the identification of the best imaging time point the evaluation of quantitative and objective technical parameters such as S/N and C/N calculations based on signal intensity measurements provide additional reliable and sufficient data.

Because the most relevant biases with regard to dose and imaging time-point were minimized by the double blind design of the clinical studies an additional independent blinded evaluation of the images (blinded reading) was deemed not to be necessary.

Dose Discussion:

During the phase I development imaging was performed in healthy volunteers (Report 5.3.4.1 A337) at doses of 10, 25, 50 and 100 µmol/kg BW. The dose of 100 µmol/kg BW was too high since susceptibility effects led – after an initial signal increase - to a transient signal loss in healthy liver tissue. The doses up to 50 µmol/kg BW, however, showed a continuous increase of signal enhancement of the liver.

These findings determined the selection of doses for further phase II trials. The first study confirmed the phase I results in patients in terms of technical efficacy but failed to show any difference between the three doses tested (12.5, 25 and 50 µmol/kg BW) for either the primary endpoint (increase in diagnostic confidence) or for all secondary endpoints (e.g. number of lesions, lesion visualization).

Therefore, another dose comparative study was performed which differed from the first study mainly as follows:

- Doses included 3, 6, 12.5 and 25 µmol/kg BW as well as a placebo control
- Comparisons were done for each dose against placebo instead of paired comparisons among all dose groups
- The study addressed more specifically the dynamic imaging phase

The results of this study indicated that a dose of 25 µmol /kg BW is sufficient but also necessary for the majority of patients if all the specific properties of Gd-EOB-DTPA are regarded. For most of the parameters the

doses of 12.5 and 25 µmol/kg BW showed a significant improvement as compared to placebo. Although no clear difference between these doses was seen for lesion detection, the dose of 25 µmol/kg BW was the only dose which fulfilled the prospectively defined success criteria in terms of good and excellent improvement in diagnostic confidence (> 55%) and showed good and excellent ratings in patients with liver cirrhosis and HCC.

Measurement of Signal Intensity:

According to the protocol, the ventral direction was to be standardized as the phase-encoding direction, and the lateral direction as the frequency direction. Measurement of the signal intensity of the lesion referring to the most probable diagnosis as specified in the primary indication, was to be made along with the SI of normal hepatic tissue and of the image background on the best representative images. These images were to be selected from the mandatory pre-contrast T1-weighted GRE sequences and from both post-contrast dynamic (up to 10 minutes) and delayed sequences (20 and 45 minutes scan), according to the following:

1. If for the primary indication more than one lesion was seen, then the investigator was to select one lesion which according to him/her was most representative of the primary indication. This lesion was to be evaluated in each sequence.

2. The lesion must have had a diameter of at least 1 cm. If in a patient all lesions regarding the primary indication were smaller than 1 cm then quantitative data were only to be recorded for the normal liver.

3. SI of one region of interest (ROI) in normal liver tissue, as close as possible to the lesion was to be measured.

4. Intensity of background noise along with standard deviation was to be measured by two ROI. These regions must have been in the same image as the lesion, and as far (1) laterally and (2) ventrally away from the lesion as possible.

5. Necrotic areas, and the periphery of lesions were to be avoided. The same ROI was to be assessed on the best pre- and post-contrast MR scans.

6. As an option, the investigator was allowed to record measurements from delayed sequences for an additional lesion (if present) that was not part of the primary indication.

Calculations of signal to noise (S/N) and contrast to noise (C/N) ratios were to be done according the following formulae :

S/N = SILiver / SIBackground

C/N = (SILesion - SILiver) / SDBackground noise

%Enhancement = [(SIpost – SIpre) / SIpre] X 100
Contrast = (SILiver - SILesion) / (SILiver + SILesion)

where SILiver is the SI in normal liver tissue, SILesion is signal intensity of the lesion, SIBackground is the SI in the image background and SDBackground is standard deviation of the background noise. Two results were to be obtained for S/N and C/N as two measurements were to be made for image background (lateral and ventral to the lesion).

MRI procedure

1. Vital signs (blood pressure and pulse rate) were to be measured immediately prior to pre-contrast MRI examination after the patient had been in the same position for at least 10 minutes.

2. Blood and urine samples were to be collected immediately prior to the pre-contrast MRI examination.

3. An intravenous saline drip through an indwelling catheter (18-20 gauge), preferably in the forearm or anticubital vein, was to be secured before the commencement of MRI examination. A place for contrast injection should have been readily accessible in this intravenous line so that contrast medium could be injected without moving the patient out of the magnet.

4. Pre-contrast MR scans were to be performed with T1-weighted gradient echo (GRE) sequence and T2-weighted FSE/TSE or SE sequences, as specified below.

5. Whether the patient received SH L 569 B or placebo was to be determined by the next available randomization number on the center's randomization list. The injection was to be prepared and given by the confidant person accordingly.

6. SH L 569 B/placebo injection was to be administered as a bolus via the pre-established intravenous line (the antecubital vein was preferred).

A volume of normal saline (0.9% NaCl provided from the individual center) sufficient to flush the venous line was to be administered immediately following the administration of contrast medium or placebo. The patient was to be observed carefully during injection. A voice or (preferably) video link was to be maintained with the patient throughout scanning. Vital signs were to be recorded again after completion of MRI procedure.

7. Post-contrast dynamic imaging was to be started with a T1-weighted GRE sequence immediately after injection using identical imaging parameters as the pre-contrast localizer scan. This scanning was to be performed on a limited imaging volume which was most representative of the primary indication. This imaging volume was to be pre-selected by the investigator before contrast administration. The timing and imaging parameters are described later on in this section.

8. Further T1-weighted GRE sequences were to be performed at 20 and 45 minutes after injection. T2-weighted FSE/TSE or SE sequence were to be performed at 20 minutes after injection. Details of the mandatory sequences are given below.

9. Any deviation from MRI procedure was to be recorded in the case report form and the reason (machine related problem or patient related problem) were to be specified.

Required pulse sequences were:

Pre-contrast sequences

1. Transverse T2-weighted SE sequence with TR/TE = 2000-3000 msec/45-60 and 90-120 msec, 2 acquisitions, matrix = 128 X 256, FOV = 350-400 mm, slice thickness = 8 mm, interslice gap 2 mm.

OR

Transverse T2-weighted FSE/TSE sequence with TR/TE = > 3000 msec/ >80 msec, 2-4 aquisitions, echo train length = 5 - 16, matrix = 192 - 256 X 256, FOV = 350 - 400 mm, slice thickness = 8 mm, interslice gap 2 mm.

2. Transverse T1-weighted GRE sequence should be performed in two or three slabs of six to eight slices each to cover the whole liver with TR/TE = 100-200 msec/4-8 msec, flip angle = 70-90°, matrix = 128 X 256, FOV = 350 - 400 mm, slice thickness = 8 mm, interslice gap 2 mm and breath hold. Alternatively, a single slab of higher slice number covering the whole liver might also have been utilized with a TR of 160 msec. The protocol emphasized the importance of the usage of the same procedure in all patients in one center. Transverse T1-weighted GRE sequence should be performed 'in phase'. For example, it was necessary to use TE of about 5 msec for 1.5 T machine and TE of about 7 msec for 1 T machine for performing this sequence "in phase".

3. Localizer transverse pre-contrast T1-weighted GRE sequence of limited imaging volume (six slices) with TR/TE = 100/4-8 msec, matrix = 128 X 256, FOV = 350 - 400 mm, slice thickness = 8 mm, interslice gap 2 mm, flip angle 70-90° and breath hold. This imaging volume was to be selected after reviewing the pre-contrast MR scans and should be most representative of the primary indication.

Post-contrast sequences

1. Dynamic (transverse) T1-weighted GRE sequence with TR/TE = 100/4-8 msec, matrix = 128 x 256, FOV = 350-400 mm, slice thickness = 8 mm, interslice gap 2 mm, flip angle = 70-90° and breath hold.

Imaging procedure

Dynamic imaging were to be started at the end of the injection of contrast medium. Subsequent images were to be acquired after 45 seconds and at 1.5, 2, 3, 4, and 5 minutes after administration of contrast medium.

Images were to be acquired again at 8 and 10 minutes after administration of contrast medium.

2. Delayed imaging with T1-weighted GRE sequences were to be performed at 20 and 45 minutes after administration of contrast medium. T2-weighted FSE/TSE sequence were to be performed at 20 minutes after injection. Identical parameters as described for pre-contrast imaging were to be used for obtaining these images.

Data Set Analyzed:

A total of 171 patients completed the treatment of contrast medium injection. Of these 171 patients, 2 patients were excluded from the preferred efficacy evaluation due to administration of an incorrect injection volume. Thus, 169 patients were included in the preferred efficacy evaluation : placebo (0.9 % NaCl) : 35 patients, 3.0 umol SH L 569 B / kg BW : 33 patients, 6.0 umol SH L 569 B / kg BW : 32 patients 12.5 umol SH L 569 B / kg BW : 34 patients 25.0 umol SH L 569 B / kg BW : 35 patients.

Overall, 87 male and 84 female were included in the study.

Table VIII. Pre Contrast Diagnostic Confidence:

	assessment of pre-contrast diagnostic confidence								sum of patients
	none		low		moderate		high		
dose group	No.	%	No.	%	No.	%	No.	%	No.
placebo	2	5.7 %	8	22.9 %	16	45.7 %	9	25.7 %	35
3.0 umol	--	--	10	30.3 %	17	51.5 %	6	18.2 %	33
6.0 umol	2	6.3 %	11	34.4 %	12	37.5 %	7	21.9 %	32
12.5 umol	--	--	7	20.6 %	20	58.8 %	7	20.6 %	34
25.0 umol	1	2.9 %	9	25.7 %	17	48.6 %	8	22.9 %	35

Table IX. Post Contrast Diagnostic Confidence:

dose group	number of patients: change in diagnostic confidence from pre- to post-contrast						sum of patients
	worsened		unchanged		improved		
	No.	%	No.	%	No.	%	No.
placebo	--	--	34	97.2 %	1	2.9 %	35
3.0 umol	1	3.0 %	17	51.5 %	15	45.5 %	33
6.0 umol	--	--	8	25.0 %	24	75.0 %	32
12.5 umol	1	2.9 %	5	14.7 %	28	82.4 %	34
25.0 umol	1	2.9 %	2	5.9 %	31	91.2 %	34 [a]

After treatment with SH L 569 B, diagnostic confidence improved increasingly with increasing dose: improvement was rated for about half of the patients (45.5 %) in dose group 3.0 umol/kg BW, in about two thirds of the patients (75.0 %) in dose group 6.0 umol/kg BW, and for 82.4 % and 91.2 % of the patients in dose groups 12.5 and 25.0 umol/kg BW, respectively. In the placebo group, diagnostic confidence remained unchanged for nearly all the patients (97.2 %) (Table IX).

Measurement of signal Intensity:

SI measurement of liver lesions and normal liver tissue was performed to show quantitatively the comparative enhancement patterns of liver lesions compared to normal liver tissue. It was determined from pre-contrast T1-weighted GRE sequences and from both post-contrast dynamic (up to 10 minutes) and delayed sequences (20 and 45 minutes scan). Calculations were made as follows : S/N = SILiver / SIBackground

C/N = (SILesion - SILiver) / SDBackground noise %Enhancement = [(SIpost – Sipre) / SIpre] X 100 Contrast = (SILiver - SILesion) / (SILiver + SILesion)

where SILiver is the SI in normal liver tissue, SILesion is signal intensity of the lesion (lesion regarding primary indication), SIBackground is the SI in the image background and SDBackground is standard deviation from the background noise. Two results were obtained for S/N and C/N as two

measurements were made for image background (lateral and ventral to the lesion).

Pre- and T1GRE delayed post-contrast sequences :

Signal-to-noise ratio (S/N = SILiver / SIBackground)

T1GRE delayed sequences revealed an increase of S/N ratio from pre-MRI to 20-minutes post- MRI in all dose groups for lateral as well as for ventral measurement. The median values of S/N ratio at 20-minutes post-MRI increased with increasing dosage from 3.0 to 25.0 umol/kg BW. A further increase at 45 minutes post-MRI could be observed only in dose groups 12.5 and 25.0 umol/kg BW from lateral measurement, and in dose groups 3.0 and 6.0 umol/kg BW from ventral measurement. However, this second increase was much lower.

Table X. S/N Ratio from Pre and Post Contrast Images:

dose group	S/N ratio (median values)					
	lateral			ventral		
	pre-MRI	20 min post	45 min post	pre-MRI	20 min post	45 min post
placebo	15.50	15.83	15.46	13.46	14.68	15.54
3.0 umol	16.91	18.48	17.84	14.65	17.15	17.50
6.0 umol	16.02	20.95	20.80	15.89	17.86	19.09
12.5 umol	15.97	21.64	22.33	15.80	20.52	19.75
25.0 umol	15.55	23.85	25.37	16.83	23.66	23.47

% Enhancement (Delayed Sequence):

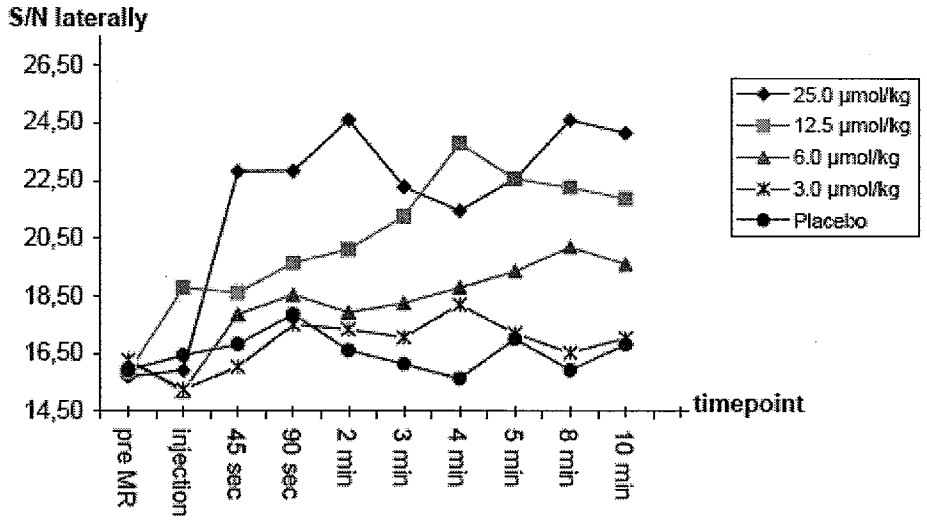
%Enhancement refers to T1 GRE measurement of the liver.

The median values for enhancement increased with increasing dosage at both time-points (20 minutes and 45 minutes post-MRI). An increase from 20-minute post-MRI to 45-minute post- MRI was observed only in the dose group 6.0 umol/kg BW.

Signal to Noise ratio (dynamic imaging) measured laterally:

In dose groups 12.5 and 25.0 umol/kg BW, a strong increase in signal-to-noise-ratio was noticed from lateral as well as ventral measurement. This increase appeared directly after injection in dose group 25.0 umol/kg BW, whereas in dose group 12.5 umol/kg BW, the increase was relatively constant over time. In dose group 6.0 umol/kg BW, only a small increase of S/N ratio was noticed. In dose group 3.0 umol/kg BW, values for S/N ratio scattered around the pre-value.

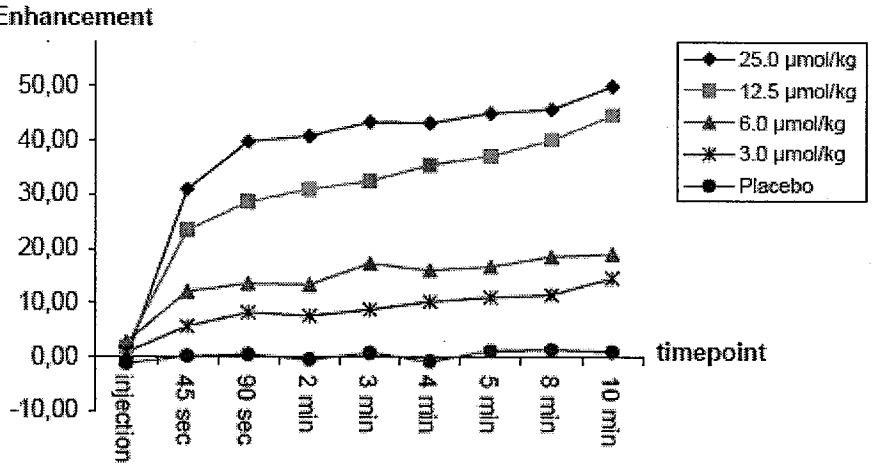
Figure X. Signal to noise vs time ratio for various doses tested



%Enhancement (%Enhancement = [(SIpost – SIpre) / SIpre] X 100)

In all dose groups, %enhancement increased over time (Figure XI). The extent of the increase was most pronounced in dose groups 12.5 and 25.0 umol/kg BW.

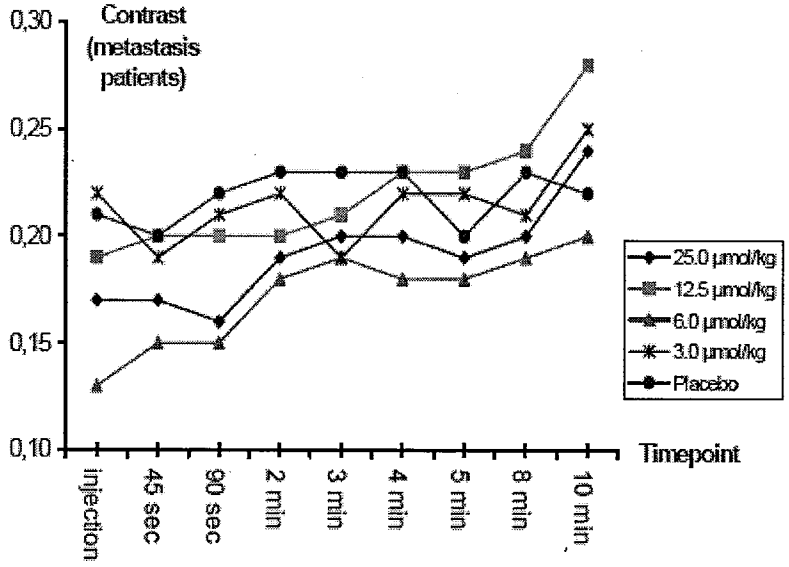
Figure XI. % Enhancement over time for different doses



Contrast (Contrast = (SILiver - SILesion) / (SILiver + SILesion))

In metastasis patients, values for contrast increased with time in dose groups 6.0, 12.5 and 25.0 umol/kg BW (Figure XII). In dose group 3.0 umol/kg BW, the values for contrast varied around the baseline value as in the placebo group. In HCC patients, values for contrast increased with time in dose groups 6.0 and 12.5 umol/kg BW. In dose group 25.0 umol/kg BW, a sharp increase was observed at 3 minutes after injection; however, the course over time was irregular in this dose group. In dose group 3.0 umol/kg BW, values varied around baseline value.

Figure XII. Contrast in metastatic patients with dose



Efficacy Conclusion:

The comparison of the doses tested in this study showed that the improvement of most of the efficacy parameters such as diagnostic confidence, visual evaluation, lesion detection, enhancement of hepatic vessels during dynamic imaging and intralesional contrast behavior increased with increasing dose. Regarding measurement of signal intensity, signal-to-noise ratio and %enhancement increased as well with increasing dose, whereas an increase regarding the parameter 'contrast' was observed only in the two highest dose groups, 12.5 and 25.0 umol/kg BW. The strongest increase for contrast-to-noise ratio was observed in the dose group 12.5 umol/kg BW.

Regarding the change in diagnostic confidence (primary variable) and visual evaluation, there was a statistically significant difference versus placebo for dose groups 12.5 and 25.0 umol/kg BW considering the changes in terms of good or excellent improvement, and for dose groups 6.0, 12.5 and 25.0 umol/kg BW considering all six levels of change (minimal/moderate/good/excellent improvement; unchanged; worsened).

The comparison of contrast-enhanced dynamic MRI using SH L 569 B vs. extracellular contrast medium revealed comparable findings particularly in dose group 25.0 umol/kg BW : the findings were comparable in 1/6 patients

(placebo group); in 0/5 patients (3.0 umol); in 2/7 patients (6.0 umol); in 3/9 patients (12.5 umol); in 4/5 patients (25.0 umol).

Diagnostic confidence :

Diagnostic confidence improved increasingly with increasing dose, with the highest percentage of improvement in dose groups 12.5 and 25.0 umol/BW (82.4 %; 91.2 % of patients). Good or excellent ratings of improvement were given only in the three highest dose groups 6.0, 12.5, and 25.0 umol/kg BW (9.4 %; 41.2 %; 67.7 % of patients). The change in diagnostic confidence (primary variable) revealed a statistically significant difference versus placebo ($p < 0.001$) for dose groups 12.5 and 25.0 umol/kg BW considering good or excellent improvement. There was no statistically significant difference between dose groups 3.0 and 6.0 umol/kg BW versus placebo group. The change in diagnostic confidence considering all six levels of change (minimal, moderate, good, excellent improvement; unchanged; worsened) revealed a statistically significant difference ($p < 0.05$) for dose groups 6.0, 12.5 and 25.0 umol/kg BW versus placebo. There was no statistically significant difference between dose group 3.0 umol/kg BW and the placebo group.

Subgroup analysis for patients with metastasis or HCC as final diagnosis (primary indication) revealed an increasing number of patients with good or excellent improvement with increasing dose in both subgroups.

Visual evaluation :

Visual evaluation, i.e. visualization, delineation and contrast, improved increasingly with increasing dose, and within each dose group with time (20-minute to 45-minute post-MR images). Good or excellent ratings of improvement were recorded only for dose groups 6.0, 12.5, and 25.0 umol/kg BW (10-13 %; 34-42%; 53-58 % of patients). Considering good or excellent improvement in visual evaluation, there was a statistically significant difference ($p < 0.05$) for dose groups 12.5 and 25.0 umol/kg BW versus placebo. There was no statistically significant difference versus placebo for dose groups 3.0 and 6.0 umol/kg BW. Considering all six levels of evaluation (minimal, moderate, good, excellent improvement; unchanged; worsened), there was a statistically significant difference ($p < 0.05$) versus placebo for dose groups 6.0, 12.5 and 25.0 umol/kg BW, but not for dose group 3.0 umol/kg BW.

Measurement of signal intensity :

Signal-to-noise ratio (S/N) : T1GRE delayed sequences revealed an increase of S/N ratio from pre-MRI to 20-minute post-MRI for all dose groups (laterally as well as ventrally). The median values of S/N ratio increased with increasing dose. A further slight increase at 45-minute post-MRI could be observed in dose groups 3.0 and 6.0 umol/kg BW (ventrally) and dose groups 12.5 and 25.0 umol/kg BW(laterally). From dynamic imaging, a small increase of S/N ratio was recorded for dose group 6.0 umol/kg BW, and a strong increase in dose groups 12.5 and 25.0 umol/kg BW.

Contrast-to-noise ratio (C/N) : T1GRE delayed sequences revealed an increase of C/N ratio from pre-MRI to 20-minute post-MRI in both, metastasis and HCC patients, in all dose groups with just one exception (HCC patients, ventral measurement in dose group 6.0 umol/kg BW). The strongest increase was observed for dose group 12.5 umol/kg BW for both subgroups. A further increase at 45-minute post-MRI could be observed in both subgroups with only a few exceptions (3.0 umol/kg BW: values varying around baseline value in metastasis patients, and decreased from ventral measurement in HCC patients; 12.5 umol/kg BW: values decreased from lateral measurement in HCC patients). From dynamic imaging, C/N ratio increased with time in dose groups 6.0, 12.5 and 25.0 umol/kg BW.

%Enhancement : T1GRE delayed sequences revealed an increase of %enhancement with increasing dose at both delayed timepoints. A further increase from 20-minute to 45-minute post-MRI was observed only in dose group 6.0 umol/kg BW. From dynamic imaging, %enhancement increased over time in all dose groups. The extent of the increase was most pronounced in dose groups 12.5 and 25.0 umol/kg BW.

Conclusions:

In this multicenter double-blind, randomized, placebo-controlled dose-ranging study, the safety, tolerability and efficacy of four doses of SH L 569 B given as a single-dose bolus injection were evaluated in comparison to placebo in patients with known focal liver lesions. Of 173 patients enrolled in the clinical study, 171 patients received SH L 569 B or placebo injection, and of these 171 patients, 169 patients were included in the preferred analysis.

The efficacy was evaluated by qualitative and quantitative parameters. The change in diagnostic confidence regarding the primary indication (i.e. lesion type evaluated) when all relevant pre- and post-contrast MR scans were compared was chosen as primary efficacy variable. Diagnostic confidence was based on the complete clinical picture for which the patient was referred to MRI and in particular on the information available on MR scans regarding the primary indication including number, size and location of lesions, visual evaluation, characterization of lesions, and change in diagnosis. Any additional and/or more detailed information or strengthening of the impression of one of the above parameters was bound to change diagnostic confidence.

Diagnostic confidence is a subjective parameter; however, in clinical situations it is relevant to determine the confidence of the radiologist as to whether the images in fact represent the truth. Diagnostic confidence conceptualizes the diagnostic thinking efficacy, and links technical and diagnostic efficacy of a contrast agent with the therapy for the patient.

All the components of diagnostic confidence as described above were evaluated as secondary efficacy variables. In addition, dynamic imaging, intralesional contrast behavior, signal intensity of liver lesion(s) and normal liver tissue, and patient management (therapy and investigation) were assessed.

A first phase II study, which was performed prior to this phase II study, revealed no significant difference with regard to good and excellent improvement of diagnostic confidence as primary endpoint nor for any of the secondary efficacy endpoints between the three dose levels tested in that study, i.e. 12.5, 25.0 and 50.0 umol SH L 569 B /kg BW. Thus, the lowest effective dose could not be determined in that study. The present study was thus intended to define better the dose response by testing lower doses in addition. However, the results which were obtained in the first study for good and excellent improvement of diagnostic confidence (12.5 umol: 54.2 %; 25.0 umol: 54.1 %; 50.0 umol: 60.0 %) were still considered to be desirable and the sample size was planned to identify the lowest dose leading to good or excellent improvement of diagnostic confidence in at least 55 % of the patients. In case this prospectively determined criterion was not met, the dose decision was to be based not only on the results of hypothesis testing but also on the information on secondary variables.

The actual results revealed for the change in diagnostic confidence as the primary endpoint a statistically significant difference versus placebo ($p< 0.001$) for dose groups 12.5 and 25.0 umol/kg BW with ratings for good or excellent improvement of 41.2 %, and 67.7 % of the patients. Thus, the prospectively defined decision criterion of 55 % improvement as the required cut-off value was only obtained in the dose group 25.0 umol/kg BW. This overall result was also seen for the subgroup of patients with HCC whereas in patients with metastases the cut-off value was reached already at 12.5 umol/kg BW. With regard to the intended clinical use of SH L 569 B, to characterize lesions with an essentially similar reliability as extracellular MR contrast agent and to detect additional lesions, a dose had to be selected which provides robust and reproducible results for all lesion types and not only metastases. Based on the analysis of the primary endpoint, this can only be achieved by a dose of 25.0 umol/kg BW.

4.3 Consult Review: N/A

4.4 Cover Sheet and OCP Filing Form:

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	22090	Brand Name	Primovist (Gd-EOB-DTPA)
OCPB Division (I, II, III, IV, V)	DCP V	Generic Name	
Medical Division	Division of Medical Imaging and Hematology Drug products	Drug Class	
OCPB Reviewer	Christy S. John, Ph.D.	Indication(s)	For detection of hepatocellular carcinoma using MRI
OCPB Team Leader	Young Moon Choi, Ph.D.	Dosage Form	Clear Liquid
		Dosing Regimen	25 micromol/kg
Date of Submission	July 5, 2007	Route of Administration	IV Injection
Estimated Due Date of OCPB Review	February, 2008	Sponsor	Bayer health care Pharmaceutuicals
PDUFA Due Date	May 2008	Priority Classification	1 S
Division Due Date	March 2008		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:	X			
Isozyme characterization:	X			
Blood/plasma ratio:	X			
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:	X			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:	X			
hepatic impairment:	X			
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?		The application is filable from Clinical Pharmacology perspective.
Comments sent to firm ?		The class warning for Nephrogenis Systemic Fibrosis (NSF) is missing in the label. PM is going to notify the sponsor.
QBR questions (key issues to be considered)	Is dose adjustment necessary in patients with severe renal and hepatic impairment? Should the drug be contraindicated in above population?	
Other comments or information not included above		
Primary reviewer Signature and Date	Christy S. John, Ph.D	
Secondary reviewer Signature and Date	Young Moon Choi, Ph.D.	

APPEARS THIS WAY
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christy John
5/7/2008 01:52:52 PM
BIOPHARMACEUTICS

Young-Moon Choi
5/7/2008 01:56:03 PM
BIOPHARMACEUTICS

Atiqur Rahman
5/7/2008 03:07:06 PM
BIOPHARMACEUTICS