Australian Government
Department of Health
Therapeutic Goods Administration

# AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Gadobutrol

Proprietary Product Name: Gadovist

Sponsor: Bayer Australia Ltd

**16 July 2014**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

# About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

# Contents

# List of commonly used abbreviations

| Abbreviation | Meaning |
|---|---|
| AE | Adverse event |
| AE,ur | Amount excreted into urine during the complete sampling period |
| AE,ur(t1-t2) | Amount excreted into urine from sampling time point t1 to sampling time point t2 |
| APTT | Activated partial thromboplastin time |
| AUC | Area under the concentration-time plasma curve |
| AUC(0-tlast) | AUC from time 0 to last data point |
| AUCM | Area under the first moment curve |
| BMI | Body Mass Index |
| BW | Body Weight |
| CA | Compartmental analysis |
| CI | Confidence interval |
| CL | Total body clearance |
| Clast | Last concentration value above lower limit of quantitation, directly taken from analytical data |
| CLR | Total renal body clearance |
| Cmax | Maximum observed drug concentration |
| CNS | Central nervous system |
| CV | Coefficient of variation |
| D | Dose |
| ECG | Electrocardiogram |
| FDA | Food and Drug Administration |
| Gd | Gadolinium |
| GDD | Global Data Dictionary |

| Abbreviation | Meaning |
|---|---|
| ICH GCP | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice |
| IEC | Independent Ethics Committee |
| LLOQ | Lower limit of quantification |
| MCH | Mean corpuscular hemoglobin |
| MCV | Mean corpuscular volume |
| MR | Magnetic resonance |
| MRI | Magnetic resonance imaging |
| MRT | Mean residence time |
| NCA | Non compartmental analysis |
| NSF | Nephrogenic Systemic Fibrosis |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| SAE | Serious adverse event |
| SD | Standard deviation |
| $t_{1/2}$ | Half-life associated with the terminal slope |
| $t_{1/2\ alpha}$ | Half-life associated with the first exponent of a polyexponential equation |
| $t_{1/2\ beta}$ | Half-life associated with the second exponent of a polyexponential equation |
| $t_{last}$ | Time of last concentration above LLOQ, directly taken from analytical data |
| Vc | Apparent volume of distribution of central compartment |
| VSS | Apparent volume of distribution during steady state |

# 1. Introduction

Bayer Australia Pty Ltd has applied to extend the indications for Gadovist® (gadobutrol), an agent for Magnetic resonance imaging (MRI). Gadovist® is approved for diagnostic purposes only. It is indicated in adults, adolescents and children aged 2 years and older for:

· Contrast enhancement in cranial and spinal MRI

- Use in first–pass MRI studies of cerebral perfusion
- Contrast enhancement (CE) in magnetic resonance angiography (MRA)
- CE MRI of other body regions: Liver and kidneys.

The sponsor has applied for an extension of indication for adults, adolescents and children aged 2 years or older which include:

- Contrast enhancement in whole body MRI including head and neck region, thoracic space, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus), retroperitoneal space (kidney), extremities and musculoskeletal system
- Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.

### 1.1. Clinical rationale

MRI is an established imaging technique used in the diagnosis of patients with many diseases including vascular abnormalities, parenchymal organ disorders, and neurological, breast, musculoskeletal and cardiovascular disorders. Gadovist® is an aqueous solution of gadobutrol containing gadolinium, a paramagnetic metal which shortens relaxation times (T1 and T2) of hydrogen protons. Gadovist® is one of a class of gadolinium-based contrast agents which enhance organ lesions or blood vessel structures allowing the detection of abnormal vascularity during first pass imaging, leakage through the blood brain barrier, and distribution through the extracellular space. Gadovist® has been approved worldwide since 1998 for use in a limited number of indications including CNS, liver and kidney imaging, and imaging of cerebral perfusion and CE-MRA. However, other ECCMs such as Dotarem®, Prohance®, Magnevist® and Omniscan® have been approved for whole body imaging and are widely used for the detection of multiple pathologies in organs such as breast, liver, kidneys, pancreas, head and neck, and prostate. All Gd-based ECCMs share similar PK/PD characteristics and diagnostic accuracy. The sponsor proposes that Gadovist® is non-inferior to other marketed products and seeks to extend the limited current indications to whole body use, including cardiac imaging.

# 2. Contents of the clinical dossier

### 2.1. Scope of the clinical dossier

The submission contains the following clinical information:

- A comparative PK study (308183) of Gadovist® in elderly and non-elderly subjects.
- Two identical pivotal Phase III studies (91743 and 91782) evaluating the diagnostic performance of Gadovist® in CE-MRI of the breast.
- A pivotal Phase III study (13297) comparing whole body imaging with Gadovist® and Magnevist® in Asian patients.
- A post hoc analysis of a previously evaluated study (94055/99012) providing further evidence of the performance of Gadovist® in different body regions.
- A Phase II dose-finding study in myocardial perfusion MRI.
- A systematic literature review of all indications other than those currently approved for Gadovist® but in the same range of indications as currently approved for Magnevist® and Dotarem®.
- An Integrated Summary of Safety from clinical studies and post-marketing surveillance.

### 2.2. Paediatric data

The submission did not include paediatric data.

### 2.3. Good clinical practice

All studies were performed according to the principles of ICH GCP and GLP.

# 3. Pharmacokinetics

### 3.1. Studies providing pharmacokinetic data

Summaries of a pre-clinical PK study in rabbits (KM12004) and a PK study in healthy non-elderly and elderly subjects (308183) were reviewed. Neither of the PK studies had deficiencies that excluded the results from consideration.

### 3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional studies unless otherwise stated.

#### 3.2.1. Physicochemical characteristics of the active substance

No new data submitted.

#### 3.2.2. Pharmacokinetics in healthy subjects

##### *3.2.2.1. Absorption*

*3.2.2.1.1. Sites and mechanisms of absorption*

Not applicable.

*3.2.2.1.2. Bioavailability*

Not applicable.

#### 3.2.3. Pharmacokinetics in the target population

No new data submitted.

#### 3.2.4. Pharmacokinetics in other special populations

##### *3.2.4.1. Pharmacokinetics in subjects with impaired hepatic function*

No new data submitted.

##### *3.2.4.2. Pharmacokinetics in subjects with impaired renal function*

No new data submitted.

##### *3.2.4.3. Pharmacokinetics according to age*

Study 30183 assessed PK behaviour in healthy elderly subjects aged ≥65 years compared with non-elderly subjects aged 18-45 years. In healthy elderly men and women CL was reduced by approximately 25% and 35%, respectively, compared with non-elderly subjects. AUC was increased by 33% and 54%, respectively, and $t_{1/2}$ was increased by approximately 33% and 58%, respectively.

##### *3.2.4.4. Pharmacokinetics related to genetic factors*

No new data submitted.

#### *3.2.4.5. Pharmacokinetics in other special populations*

No new data submitted.

### 3.2.5. Pharmacokinetic interactions

#### *3.2.5.1. Pharmacokinetic interactions demonstrated in human studies*

No new data submitted.

#### *3.2.5.2. Clinical implications of in vitro findings*

Not applicable.

## 3.3. Evaluator's overall conclusions on pharmacokinetics

A pre-clinical study in rabbits (KM12004) demonstrated identical PK behaviour for Gadovist®, Magnevist® and Dotarem®. There was equivalent organ distribution in all the organs examined, supporting the whole body indication in man. A comparison of PK in elderly and non-elderly subjects demonstrated that exposure is modestly increased in the elderly population. The results complete the PK profile of the marketed product although they have no direct relevance for the proposed new indication.

# 4. Pharmacodynamics

## 4.1. Studies providing pharmacodynamic data

No new data submitted.

# 5. Dosage selection for the pivotal studies

The approved dose of Gadovist® was used in all studies.

# 6. Clinical efficacy

## 6.1. Indication 1:

Contrast enhancement in whole body MRI including head and neck region, thoracic space, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus), retroperitoneal space (kidney), extremities and musculoskeletal system.

### 6.1.1. Pivotal efficacy studies

#### *6.1.1.1. Study 13297*

##### *6.1.1.1.1. Study design, objectives, locations and dates*

This was a Phase III, multicentre, multinational, randomised, controlled, single-blind, group comparison of Gadovist® (GAD) and Magnevist® (MAG) following a single injection in Asian patients referred for contrast-enhanced MRI (CE-MRI) of body regions, including breast, heart, abdomen, kidney, pelvis and extremities. The study was conducted at 17 centres in Japan, S. Korea and China. The first patient was recruited in January 2010 and the study completed in April 2011. The objective of the study was to demonstrate the non-inferiority of combined unenhanced and GAD-enhanced MRI compared to combined unenhanced and MAG-enhanced MRI measured by the degree of contrast enhancement, assessment of border delineation and

the internal morphology of lesions. A total of 360 patients aged at least 20 years were planned to receive either GAD or MAG as a comparator with 180 patients in each group. At least 40 patients were to be examined in each body region (breast, heart, abdomen, kidney, pelvis, or extremities) with a maximum of 80 patients in any one body region. The final clinical diagnosis (SOR, standard of reference) was provided by the treating physician at each site for each patient. The SOR was based on all clinical data including pathology when available for up to 3 months after the MR diagnosis.

GAD 0.1 mmol/kg BW was given by a single IV injection at a rate of 1.5-2 mL/sec followed by a 10 mL N saline flush given at the same rate. MAG was delivered in the same manner at the same dose at the approved rate of 2-3 mL/sec. MR images were obtained before administration of the CAs (unenhanced MRI) consisting of at least two sequences (T1-weighted [T1w] and T2-weighted [T2w]); following GAD injection consisting of steady-state imaging (T1w); or following MAG injection consisting of steady-state imaging (T1w). In addition, dynamic sequences (T1w) were performed to image the breast, abdomen, kidney, pelvis, or extremities. The complete MR image sets were evaluated by three independent blinded readers in addition to the clinical investigators. Patient safety was assessed by monitoring vital signs, physical examination, and clinical laboratory parameters. Safety observations including adverse event monitoring were continued for 24 ± 4 hours after CA injection with a follow-up phone call on Day 3. The schedule of procedures is shown in Table 1 and the imaging protocol is shown in Table 2. Standardised MR diagnoses were recorded and standardised recording of malignant lesions was performed.

**Table 1: Schedule of procedures**

| | Enroll-ment | Day -1 | Day 0 | | | | | | Day 1 | Day 3 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Base-line | Before inj. | Inj. | After inj. | 45(±15) min | 6(±2) hours | 24(±4) hours | |
| Eligibility | X | | X | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Prior/concomit-ant therapy | | ← | — | — | — | — | — | — | — | → |
| Medical/surgical history | X | | X | | | | | | | |
| Demographic | | | X | | | | | | | |
| MRI scan | | | | X | | X | | | | |
| AE monitoring | | ← | — | — | — | — | — | — | → | |
| Laboratory test | | | X | | | | | | X | |
| Vital signs | | | X | | | | X | X | X | |
| Physical exam. | | | X | | | | X | X | X | |
| AE confirmation | | | | | | | | | | X* |

*: Subjects were checked whether delayed drug reaction had occurred by phone call on Day 3.
Abbreviations: MRI, Magnetic resonance imaging; AE, adverse event

**Table 2: Study 13297 Imaging protocol**

| Region | Unenhanced MRI | Enhanced MRI | Plane |
|---|---|---|---|
| Breast | • T1w-GRE<br>• T2w-FSE with fat suppression | • T1w-SE<br>• 3D-GRE with fat suppression (dynamic)<br>• Bilateral imaging | • Axial |
| Heart | • T1w | • T1w<br>• IR (delayed at 10 (± 2) min post injection.) | • Short axis<br>• Long axis |
| Abdomen | • T1w-GRE (double echo)<br>• T2w- FSE | • T1w-GRE (double echo)<br>• 3D-Flash with fat suppression (dynamic) | • Axial |
| Kidney | • T1w-GRE<br>• T2w-FSE | • 2D-Flash or 3D-GRE with fat suppression (dynamic)<br>• T1w-GRE | • Axial<br>• Coronal<br>• Sagittal as applicable |
| Pelvis | • T1w-SE<br>• T2w-FSE | • 2D-Flash or 3D-GRE with fat suppression (dynamic)<br>• T1w-SE | • Axial<br>• Short axis (uterus) |
| Extremities (bone/soft tissue) | • T1w- SE<br>• T2w-FSE | • 2D-Flash or 3D-GRE with fat suppression (dynamic)<br>• T1w-SE | • Axial<br>• Coronal<br>• Sagittal as applicable |

Abbreviations: T1w, T1-weighted; T2w, T2-weighted; 2D, 2 dimensional; 3D, 3 dimensional; GRE, gradient-recalled echo; SE, spin echo; FSE, fast spin echo; Flash, Fast low angle shot; IR, inversion recovery

*6.1.1.1.2. Inclusion and exclusion criteria*

The main inclusion criteria were patients aged at least 20 years referred for MRI based on current clinical symptoms and with a negative pregnancy test. The main exclusion criteria were pregnant or nursing mothers; any investigational product in the preceding 2 weeks; any previous GAD study; contra-indications to MRI or Gd-containing CAs; a history of any severe allergic or anaphylactic reaction; received any contrast agent within 24 hours of the study MRI; GFR <30mL/min/1.73m$^2$ in the preceding 4 weeks; clinically unstable; severe cardiovascular disease; patients with acute renal insufficiency of any severity; and contra-indications to MAG.

*6.1.1.1.3. Study treatments*

A single IV dose of GAD (1.5-2 mL/sec) or MAG (2-3 mL/sec) was administered at a dose of 0.1 mmol/kg BW followed by a 10 mL N saline flush given at the same rate.

*6.1.1.1.4. Efficacy variables and outcomes*

The main efficacy variables were:

Degree of contrast enhancement using a 4-point scale:

1. No lesion was not enhanced
2. Moderate lesion was weakly enhanced
3. Good lesion was clearly enhanced
4. Excellent lesion was clearly and brightly enhanced

Border delineation using a 4-point scale:

1. None no or unclear delineation of the lesion boundaries
2. Moderate some aspects of border delineation covered
3. Good almost clear, but not complete delineation
4. Excellent clear, and complete delineation

Internal morphology using a 3-point scale:

1. Poor the structure and internal morphology of the lesion were poorly visible
2. Moderate the structure and internal morphology of the lesion were partially visible
3. Good the structure and internal morphology of the lesion were sufficiently visible

The primary efficacy outcome was non-inferiority of combined unenhanced and GAD-enhanced MRI compared with combined unenhanced and MAG-enhanced MRI.

Other efficacy outcomes included:

- Improvement of combined unenhanced and GAD-enhanced MRI compared with combined unenhanced and MAG-enhanced MRI
- Comparable efficacy between GAD and MAG measured by an exact match of the MR and clinical diagnoses, and sensitivity and specificity for detection of malignant lesions in all regions other than the heart
- Confidence in the diagnosis using a 4-point scale (not confident, somewhat confident, confident, very confident).

*6.1.1.1.5. Randomisation and blinding methods*

The study drug (GAD or MAG) was randomised and stratified by body region and suspected disease. After determining the region to be examined, randomisation was performed by the investigator using IVRS/IWRS. The investigators were unblinded to the study treatment but the patients were not informed of the study drug identity. Independent blinded reading sessions were performed by three experienced radiologists who were not affiliated to the study centres or involved in the conduct of the trial. The images used for blinded evaluation did not contain any clinical data or information regarding the study centre, the scanner manufacturer, the CA, or imaging times.

*6.1.1.1.6. Analysis populations*

The Safety Analysis Set (SAS) consisted of all randomised patients except those who did not receive an investigational CA (n=363). The Full Analysis Set (FAS) was patients who received study CA but did not have efficacy data available (e.g. patients who did not complete the MRI, or whose images were considered not assessable due to poor quality) (n=359). The Per Protocol Set (PPS) consisted of patients who completed the study without major protocol deviations (n=346).

*6.1.1.1.7. Sample size*

The assumptions for sample size calculations were:

- The SD was 2.5 in terms of the total score of primary variables
- The non-inferiority margin was 1.2
- The true total score of GAD was equal to MAG under the alternative hypothesis
- The 95% CI of the difference between GAD and MAG was calculated assuming that the standardised difference followed a t-distribution
- The non-inferiority of GAD compared with MAG was established if the lower 95% confidence limit was larger than -1.2, equivalent to a two-sample t-test with a non-inferiority margin of 1.2 and a one-sided significance level of 0.025.

Based on these assumptions, a total sample size of 324 patients (162 in each group) had 99% power. Assuming a 10% exclusion rate, the planned study population was 360 patients with 180 patients in each group.

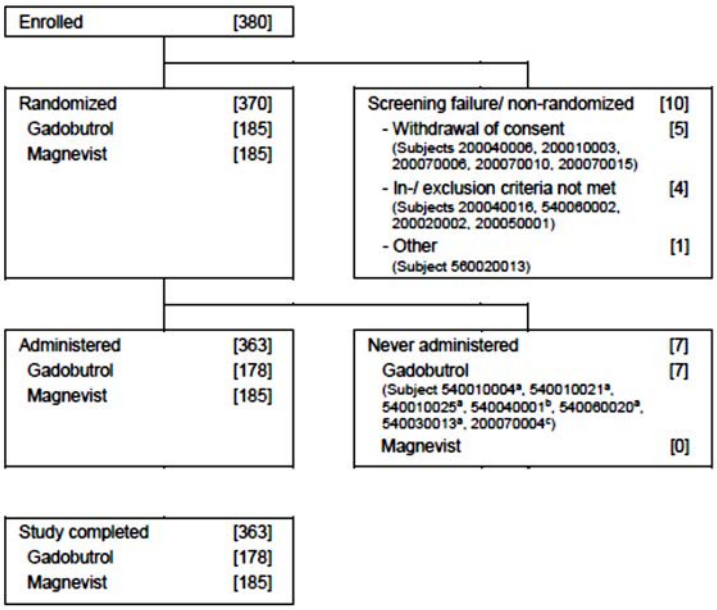
*6.1.1.1.8. Statistical methods*

Statistical evaluation was performed using SAS 9.1 or higher. Scores for each variable were averaged across lesions by patient and by investigator/blinded reader, respectively. The total scores of three primary variables by investigator/blinded reader were used for secondary analyses of primary variables. The 95% CI of the difference of the total scores of the average blinded reader between GAD and MAG were calculated for the FAS and PPS. Descriptive statistics of the total scores were shown for the PPS by study groups. The number of lesions, detection of malignant lesions, MR diagnosis, and confidence in diagnosis for the PPS were analysed descriptively. Differences in the number of lesions detected between combined MR images and unenhanced MR images for the PPS were analysed descriptively. Matching of the MR diagnosis with the SOR for the PPS was calculated by the investigator, blinded readers and study groups. Sensitivity and specificity for detection of malignant lesions compared to the SOR were calculated by the investigator, blinded readers and study groups. Non-inferiority of GAD to MAG was assumed if the lower confidence limit of the difference was greater than -1.2.

*6.1.1.1.9. Participant flow*

A total of 380 patients were enrolled of whom 370 patients were randomised (185 in each group). A total of 363 patients completed the study (178 GAD, 185 MAG). Seven patients in the GAD group were withdrawn before receiving the study drug, due to withdrawal of consent in 5 patients. Additional details are shown below in Figure 1.

**Figure 1: Participant flow**




*6.1.1.1.10. Major protocol violations/deviations*

A total of 79 patients (21.4%) had at least one minor protocol deviation and 15 (4.1%) patients had at least one major deviation. MRI procedure deviations were recorded in 10 patients: 3 patients were given excluded concomitant medications, and one patient had severe cardiovascular disease at entry. Two patients received <90% or >110% of the required dose. They were excluded from the PPS but included in the FAS.

*6.1.1.1.11. Baseline data*

The demographics and baseline characteristics of the 363 patients in the SAS indicated that all patients were Asian and the majority (52.3%) were female. Mean age was 55.6 years, mean height was 162.7 cm, and mean weight was 62.4 kg. The demographics were similar in the two

treatment groups. A total of 82.1% of patients had a previous medical or surgical history (80.9% GAD, 83.2% MAG), and 66.1% had prior or concomitant medications (66.3% GAD, 65.9% MAG).

*6.1.1.1.12. Results for the primary efficacy outcome*

The primary efficacy analysis was based on the difference in the mean (± SD) total scores of three visualisation parameters between GAD (9.39 ± 1.06) and MAG (9.34 ± 1.23) for the PPS as assessed by the average blinded reader. The mean difference between the total scores for the PPS was 0.05 ± 1.15 (95% CI: -0.195, 0.298). The non-inferiority of GAD to MAG was confirmed as the lower bound of the 95% CI was greater than -1.2.

*6.1.1.1.13. Results for other efficacy outcomes*

In the PPS, the mean total scores of the three visualisation parameters on combined images were 9.27–9.59 for GAD and 9.19–9.68 for MAG for each blinded reader, and 9.35 for GAD and 9.31 for MAG for the investigator. The lower bounds of the 95% CIs of the differences were -0.375 or above for each blinded reader, and -0.300 for the investigator. The lower bounds of the CIs of the differences were greater than -1.2 for each blinded reader and the investigator so non-inferiority was confirmed. The results of the FAS were similar to the PPS. In the FAS, the total scores on combined images were 9.38 ± 1.07 for GAD and 9.36 ± 1.22 for MAG for the average blinded reader, and 9.38 for GAD and 9.31 for MAG for the investigator. For each blinded reader, the total scores were 9.27-9.58 for GAD and 9.21-9.68 for MAG. The lower limit of the 95% CIs of the difference was -0.213 for the average blinded reader, and -0.260 for the investigator.

Inter-reader variability within the same patient and modality was tested by measuring the intra-class correlation coefficient (ICC) on the PPS (a value of 1 indicating perfect agreement and a value of 0 indicating no agreement). The ICC value for the total score of the three visualisation parameters was 0.558 for GAD and 0.504 for MAG among the blinded readers. The value on the unenhanced images was 0.525 which is considered to represent fair to good agreement. The total scores of the three visualisation parameters on unenhanced and combined images were shown. For the average blinded reader, the mean total scores increased by 2.77 after enhancement for GAD and 2.91 for MAG, and the results were consistent between the three blinded readers and the investigator. Scores of contrast enhancement on unenhanced and combined images showed comparable results between GAD and MAG for the blinded readers and the investigator for each primary variable. For the PPS, the mean scores for degree of contrast enhancement, border delineation, and internal morphology are summarised in Tables 3-5. Overall, the results were comparable between GAD and MAG for the blinded readers and the investigator.

**Table 3: Study 13297 Degree of contract enhancement**

| Reader | Gadobutrol | | | Magnevist | | |
|---|---|---|---|---|---|---|
| | Unenhanced | Combined | Difference | Unenhanced | Combined | Difference |
| Average blinded reader | 1.00 ± 0.06 (146) | 2.94 ± 0.99 (164) | 1.85 ± 1.01 (146) | 1.01 ± 0.08 (155) | 3.07 ± 0.89 (174) | 2.02 ± 0.89 (154) |
| Blinded reader 1 | 1.00 ± 0.00 (139) | 3.09 ± 1.10 (158) | 2.00 ± 1.13 (136) | 1.00 ± 0.00 (142) | 3.21± 1.00 (169) | 2.14 ± 1.03 (140) |
| Blinded reader 2 | 1.00 ± 0.00 (131) | 2.93 ± 1.12 (158) | 1.79 ± 1.14 (130) | 1.00 ± 0.00 (144) | 3.04 ± 0.99 (169) | 1.91 ± 0.99 (143) |
| Blinded reader 3 | 1.01 ± 0.17 (138) | 2.80 ± 1.06 (156) | 1.69 ± 1.07 (135) | 1.02 ± 0.25 (139) | 2.99 ± 0.98 (167) | 1.92 ± 1.02 (138) |
| Investigator | 1.00 ± 0.00 (141) | 3.01 ± 0.92 (163) | 1.95 ± 0.95 (141) | 1.00 ± 0.00 (150) | 3.10 ± 0.86 (176) | 2.07 ± 0.89 (150) |

Source: Table 14.2/50, Table 14.2/71
Values are the mean ± standard deviation (number of subjects).
PPS population (n=168 in gadobutrol group and n=178 in Magnevist group) were used for image evaluation but subjects with no lesion were excluded from the analysis.
4-point scale, 1 (no), 2 (moderate), 3 (good) and 4 (excellent), was used for assessment.

**Table 4: Study 13297 Border delineation**

| Reader | Gadobutrol | | | Magnevist | | |
|---|---|---|---|---|---|---|
| | Unenhanced | Combined | Difference | Unenhanced | Combined | Difference |
| Average blinded reader | 3.35 ± 0.62 (146) | 3.61 ± 0.45 (164) | 0.28 ± 0.54 (146) | 3.28 ± 0.63 (155) | 3.46 ± 0.61 (174) | 0.23 ± 0.56 (154) |
| Blinded reader 1 | 3.54 ± 0.65 (139) | 3.66 ± 0.55 (158) | 0.19 ± 0.68 (136) | 3.48 ± 0.68 (142) | 3.65 ± 0.56 (169) | 0.25 ± 0.66 (140) |
| Blinded reader 2 | 3.41 ± 0.63 (131) | 3.63 ± 0.53 (158) | 0.26 ± 0.63 (130) | 3.29 ± 0.71 (144) | 3.43 ± 0.70 (169) | 0.14 ± 0.72 (143) |
| Blinded reader 3 | 3.26 ± 0.75 (138) | 3.55 ± 0.62 (156) | 0.34 ± 0.74 (135) | 3.17 ± 0.81 (139) | 3.37 ± 0.90 (167) | 0.28 ± 0.77 (138) |
| Investigator | 2.69 ± 0.90 (141) | 3.52 ± 0.67 (163) | 0.88 ± 0.80 (141) | 2.72 ± 0.80 (150) | 3.45 ± 0.67 (176) | 0.83 ± 0.75 (150) |

Source: Table 14.2/57, Table 14.2/78
Values are the mean ± standard deviation (number of subjects).
PPS population (n=168 in gadobutrol group and n=178 in Magnevist group) were used for image evaluation but subjects with no lesion were excluded from the analysis.
4-point scale, 1 (none), 2 (moderate), 3 (good) and 4 (excellent), was used for assessment.

**Table 5: Study 13297 Internal morphology PPS**

| | Gadobutrol | | | Magnevist | | |
|---|---|---|---|---|---|---|
| | ıhanced | Combined | Difference | Unenhanced | Combined | Difference |
| Average blinded reader | 2.23 ± 0.41 (146) | 2.85 ± 0.24 (164) | 0.64 ± 0.45 (146) | 2.18 ± 0.34 (155) | 2.81 ± 0.28 (174) | 0.67 ± 0.39 (154) |
| Blinded reader 1 | 2.15 ± 0.54 (139) | 2.84 ± 0.35 (158) | 0.76 ± 0.59 (136) | 2.08 ± 0.45 (142) | 2.82 ± 0.41 (169) | 0.81 ± 0.51 (140) |
| Blinded reader 2 | 2.60 ± 0.48 (131) | 2.79 ± 0.38 (158) | 0.21 ± 0.58 (130) | 2.49 ± 0.47 (144) | 2.72 ±0.43 (169) | 0.22 ± 0.56 (143) |
| Blinded reader 3 | 2.06 ± 0.39 (138) | 2.93 ± 0.23 (156) | 0.87 ± 0.46 (135) | 2.03 ± 0.34 (139) | 2.95 ± 0.20 (167) | 0.94 ± 0.39 (138) |
| Investigator | 2.13 ± 0.62 (141) | 2.82 ± 0.39 (163) | 0.70 ± 0.61 (141) | 2.15 ± 0.59 (150) | 2.76 ± 0.48 (176) | 0.63 ± 0.59 (150) |

Source: Table 14.2/64, Table 14.2/85
Values are the mean ± standard deviation (number of subjects).
PPS population (n=168 in gadobutrol group and n=178 in Magnevist group) were used for image evaluation but subjects with no lesion were excluded from the analysis.
3-point scale, 1 (poor), 2 (moderate) and 3 (good), was used for assessment.

In the PPS, the number of lesions per patient detected on unenhanced and combined images for each reader, were shown. For the average blinded reader, the numbers of lesions detected were 3.26 ± 4.90 for GAD and 3.05 ± 4.24 for MAG on combined images and the results were consistent across the three blinded readers. The numbers of contrast-enhanced lesions were 1.89 ± 3.59 for GAD and 2.05 ± 2.93 for MAG and the results were consistent across readers. The number and proportions of patients whose MR diagnosis matched the SOR on unenhanced and combined images were shown. For the average reader, the proportions of patients with an exact match were 64.7% for GAD and 66.1% for MAG on combined images, and the results were consistent across readers and the investigator.

In the PPS, the sensitivity for the detection of malignant lesions compared to the SOR on unenhanced and combined images was summarised. For the average blinded reader, the sensitivity on combined images was 81.7% for GAD and 82.2% for MAG, with consistent results across readers and the investigator. The specificity for the detection of malignant lesions was shown. For the average blinded reader, the specificity on combined images was 81.8% for GAD and 78.4% for MAG and the results were consistent across readers. Confidence in diagnosis was evaluated for each patient by each blinded reader and the investigator. The proportion of patients with an evaluation of 'confident' or 'very confident' in the diagnosis was between 47.6% and 68.5% for GAD and between 50.0% and 72.5% for MAG on combined images.

The sensitivities by body region on combined images ranged from 68.3% for the abdomen and 100% for the kidney for GAD, and between 56.1% for the extremities and 98.3% for the kidney for MAG. The mean increases in the sensitivities from unenhanced images were higher for the breast (23.3% for GAD and 16.7% for MAG) compared with other regions (0.0% to 9.8% for GAD and -5.3% to 13.3% for MAG). The specificities on combined images were lower for the breast (33.3% for GAD and 27.8% for MAG) compared to the other regions (80.6% to 90.2% for GAD and 78.8% to 90.9% for MAG). The mean increases in the specificities from the unenhanced

images were lower for the breast (-29.2% for GAD and -33.3% for MAG) compared with other regions (-13.3% to 11.1% for GAD and -9.1% to 0.0% for MAG).

Scores for border delineation on unenhanced and combined images and their differences in the PPS were shown. The average blinded reader score was 3.61 ± 0.45 for GAD and 3.46 ± 0.61 for MAG. Mean scores for the three readers ranged from 3.55 to 3.66 for GAD and from 3.37 to 3.65 for MAG. The results were similar for GAD and MAG for the blinded readers and the investigator. Scores for internal morphology on unenhanced and combined images and their differences in the PPS were shown. The differences between the scores for GAD and MAG were broadly similar.

Subgroup analyses of primary and secondary efficacy variables were conducted by country, body region, country and body region, gender, age, and malignancy by SOR. There were differences by country in total scores of visualisation parameters but there were no meaningful differences between GAD and MAG. In general, the results of the subgroup analyses were consistent with the overall results and confirmed non-inferiority of GAD compared with MAG.

> **Comment:** The conclusions of the study confirm non-inferiority of GAD compared with MAG in different body regions. The study was well designed and conducted and particular care was taken to ensure consistent, blinded MRI reading. The primary efficacy endpoint was based on the difference between GAD and MAG in the total scores of three visualisation parameters in the PPS (degree of contrast enhancement, border delineation and internal morphology) as assessed by the average blinded reader. The non-inferiority margin was pre-defined as the lower confidence interval of the difference greater than -1.2 between GAD and MAG. The lower limit was greater than -1.2 for each of the three blinded readers and the investigator for the PPS and for the FAS. Evaluations of the secondary variables were consistent with the primary analysis and there were no meaningful differences in patient subgroups. Compared with unenhanced images, both contrast agents increased visualisation and diagnostic precision and no meaningful differences between GAD and MAG were observed. Differences in sensitivity and specificity between various body areas were observed. However, the diagnostic performance of GAD and MAG were comparable for each region.
>
> The study was performed in an exclusively Asian population but no racial differences have been observed in previous studies and the results can be extrapolated to other racial groups. A further justification for this conclusion based on the ICH E5 guideline is provided by the sponsor in Table 6.

**Table 6: Study 13297 ICH Guideline**

According to International Conference on Harmonisation (ICH) E5 guideline, the following properties of a compound make it less likely to be sensitive to ethnic factors:

- *Linear pharmacokinetics:* PK studies both in Caucasian (Reports 9746, B000, A21381, A40982, B 245 and A 40794) and Japanese subjects (Reports AS29 and A39759) have shown that the PK of Gadovist is linear (dose proportional) within the studied dose range.
- *A flat pharmacodynamic (effect-concentration) curve:* A comparable dose/concentration dependent increase in signal intensity was observed in Caucasian as well as in Japanese subjects evaluated by the contrast to noise ratio in CNS lesions at doses of 0.1 and 0.3 mmol/kg bw in Caucasians (Report AI86) and at doses of 0.1 and 0.2 mmol/kg bw in Japanese (Report 41119).
- *A wide therapeutic dose range*: Single doses of up to 1.5 mmol/kg bw, representing 15 times the standard dose for MRI, were well tolerated in healthy Caucasian subjects (B000). Doses up to 3 to 5 times the standard dose for MRI (0.1 mmol/kg bw) were also evaluated in healthy Japanese subjects (Report AS29) and in patients (Report AI69) and were well tolerated. Doses up to 3 times the standard dose for MRI were evaluated in Chinese subjects and were well tolerated (Report A40727).
- *Minimal metabolism or metabolism distributed among multiple pathways*: According to all available non clinical and clinical information, e.g., the studies in Caucasian (B000) and the study in Japanese subjects (Report A39759), gadobutrol is not metabolised and is therefore renally excreted as unchanged compound. Gadobutrol is eliminated fast and completely via the urine with no difference between Caucasians and Japanese subjects as representatives for the Asian ethnic group.
- *High bioavailability, thus less susceptibility to dietary absorption effects*: Gadovist is administered intravenously and therefore has a bioavailability of 100%.
- *Low potential for protein binding:* Gadobutrol is highly water soluble and protein binding is negligible (3 to 5%).
- *Little potential for drug-drug, drug-diet and drug-disease interactions*: Due to the non-chronic clinical application, lack of biotransformation [i.e., lack of involvement of CYP-450 enzymes], negligible protein binding, non-metabolisation and short half-life, any drug-drug, and drug-diet interaction potential of Gadovist is considered highly unlikely. No such interaction was observed in clinical studies.
- *Little potential for inappropriate use:* Gadovist is administered intravenously by health-care professionals only, i.e., under very controlled conditions, thus inappropriate use by subjects can be excluded.

### *6.1.1.2. Study 91743 (GEMMA-1)*

#### *6.1.1.2.1. Study design, objectives, locations and dates*

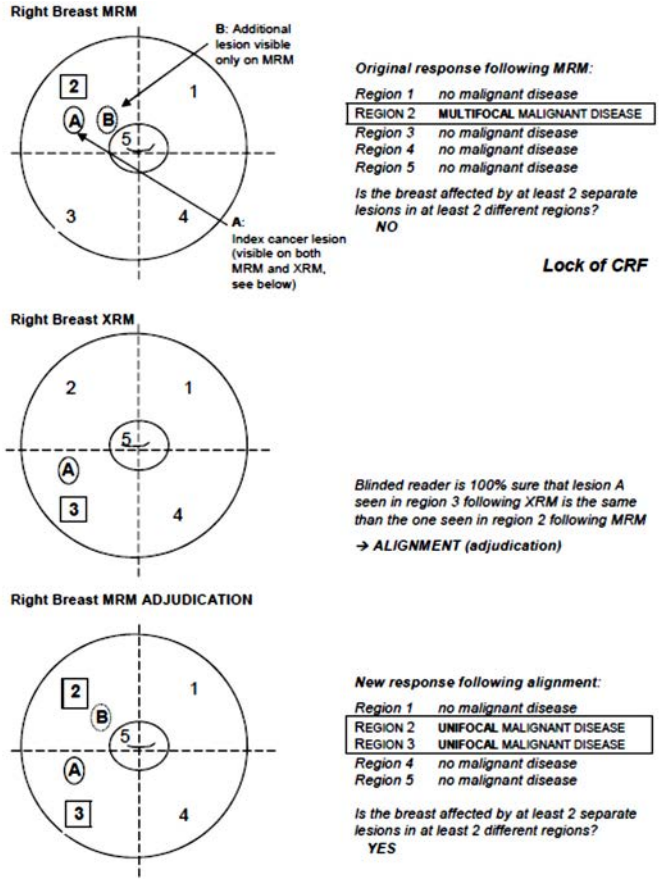
This was a Phase III, multi-centre, open-label, non-randomised study with blinded image evaluations. It was conducted at 28 centres in 7 countries (Columbia, Finland, Germany, Italy, S. Korea, Switzerland and the USA) and completed in March 2012. It was designed to demonstrate superiority of the within-patient sensitivity of combined unenhanced and GAD-enhanced MRM (CMRM) over unenhanced MRM (UMRM). It was also designed to demonstrate the specificity of CMRM in the detection of malignant versus non-malignant breast lesions. It was planned to enrol at least 440 patients with up to 60 patients at each centre. Patients with recently diagnosed histologically confirmed breast cancer after XRM were referred for breast MRI prior to breast surgery. Breast MRIs were performed using modern 1.5T scanners with dedicated breast coils to enable bilateral breast imaging. Patients received an unenhanced breast MRI, followed by a GAD-enhanced MRI. Unenhanced MRIs (consisting of T2- and T1-weighted 3D spoiled gradient echo pulse sequence) were performed, followed by GAD-enhanced scans (5 acquisitions of T1-weighted 3D spoiled gradient echo pulse sequence with acquisition time ~60 sec).

The patients stayed at the study centre for at least one hour after the MRM examination before being discharged. After 24 hours, the patients returned to the centre for a safety review. Ultrasound examinations were scheduled for patients assessed as disease free as soon as

possible after the study MRM, and before any further follow-up and subsequent breast biopsy or surgery. The study ended with the 24 hour follow-up with patients not scheduled for ultrasound investigation, and after the ultrasound investigation for patients who received them.

UMRM, CMRM and XRM image sets were evaluated in a randomised fashion by three independent, blinded readers. After evaluation of UMRM, the data were locked and evaluation of the respective XRM was performed together with UMRM. Evaluation of CMRM was then performed, followed by data lock and evaluation of CMRM and XRM. For all examinations, the evaluations of the left and right breasts were performed by regions (5 regions in each breast: 4 quadrants and the central region including nipple) as illustrated in Figure 2. For each breast region, an assessment of the presence or absence of malignancy was made. If suspected malignancy was detected, an assessment of whether it was unifocal or multifocal was made. The definition of disease status was assessed using the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) lexicon for interpretation of MRM and XRM examinations. All suspect lesions detected by MRI were required to be verified histologically. Otherwise, each breast region was assessed as disease free, either with no pathology or with a benign lesion. For regions evaluated as non-diseased without a histological confirmation, additional ultrasound evaluation was performed to confirm the MRM findings. Suspicious ultrasound findings were required to be verified histologically. The standard of truth (SoT) for the diagnostic performance of GAD-enhanced MRM was the final consensus assessment by an independent committee of two experienced breast cancer physicians who were not affiliated with the study.

**Figure 2: Example for alignment of a lesion by the blinded reader.**




*6.1.1.2.2. Inclusion and exclusion criteria*

The key inclusion criteria were: female or male patients of any ethnicity aged at least 18 years; recent histologically proven breast cancer identified after XRM of both breasts (according to

ACR and performed no longer than 6 weeks prior to enrolment); and eGFR ≥60 ml/min/1.73m$^2$. The key exclusion criteria were pregnant or lactating females; any recent other investigational products; contra-indications to MRM; a history of severe allergic or anaphylactic reactions; any contrast agent within the previous 24 hours; clinically unstable; severe cardiovascular disease; acute or chronic renal impairment; chemotherapy or hormonal therapy for breast cancer within the previous 6 months; hormone replacement therapy within 4 weeks before study drug administration; scheduled or likely to require surgery and/or biopsy within 24 hours of study drug administration; and prior excisional biopsy or breast surgery in the 6 months before enrolment and between XRM and study MRM.

*6.1.1.2.3. Study treatments*

All patients received the same treatment, a single dose of gadobutrol 0.1 mmol/kg BW given via an intravenous catheter.

*6.1.1.2.4. Efficacy variables and outcomes*

The main efficacy variables were defined by matching the readers' assessments for each breast region (by imaging modality) to the corresponding SoT assessment. For each region there were three choices: no malignant disease, unifocal malignant disease, or multifocal malignant disease present. The value of the primary efficacy variable was determined for each breast region by whether or not the category chosen by the imaging modality matched the disease state determined to be correct by the SoT.

The co-primary efficacy outcomes were (1) to demonstrate the superiority of within-patient sensitivity of combined unenhanced and GAD-enhanced MRM (CMRM) over unenhanced MRM (UMRM), and (2) to demonstrate the breast level specificity of CMRM, based on non-malignant breasts, greater than a performance threshold of 80%.

Other efficacy outcomes included:

- Breast level specificity of CMRM, based on malignant breasts, greater than a performance threshold of 50%.
- Detection of index cancers using CMRM compared with XRM, UMRM, and CMRM + XRM based on a patient level.
- Detection of additional cancer using CMRM compared with XRM, UMRM, and CMRM + XRM based on a patient level.

*6.1.1.2.5. Randomisation and blinding methods*

All patients received the same open-label treatment.

*6.1.1.2.6. Analysis populations*

A total of 440 enrolled patients was planned. Efficacy evaluations were performed using the FAS and PPS. Patients were included in the FAS if they had a valid SoT for at least one variable breast region as well as UMRM and CMRM evaluated by three independent blinded readers. Patients were excluded if the XRM was not available. The PPS included those patients who also fulfilled all major protocol requirements. Patients were excluded from the PPS for violation of inclusion/exclusion criteria; a GAD dose <90% or >110% of the required dose; MRM procedure errors; or invalid SoT procedures. The safety analysis set (SAF) consisted of all patients who received any dosage of GAD. A total of 446 patients were screened, 426 patients were included in the SAF, 390 (87.4%) patients were included in the FAS, and 335 (75.1%) patients were included in the PPS.

*6.1.1.2.7. Sample size*

The sample size was based on a 2-tailed clustered McNemar test at the 0.05 significance level. A sample size of 365 patients was required for 80% power, using the estimates of 0.70 and 0.62

for categorical accuracy for CMRM plus XRM and UMRM plus XRM, respectively, a correlation ϕ=0.10, and a substantial intra-class correlation coefficient of 0.70 for the breast regions within each patient. An additional 75 patients were planned to account for patients who did not meet the criteria for efficacy analysis.

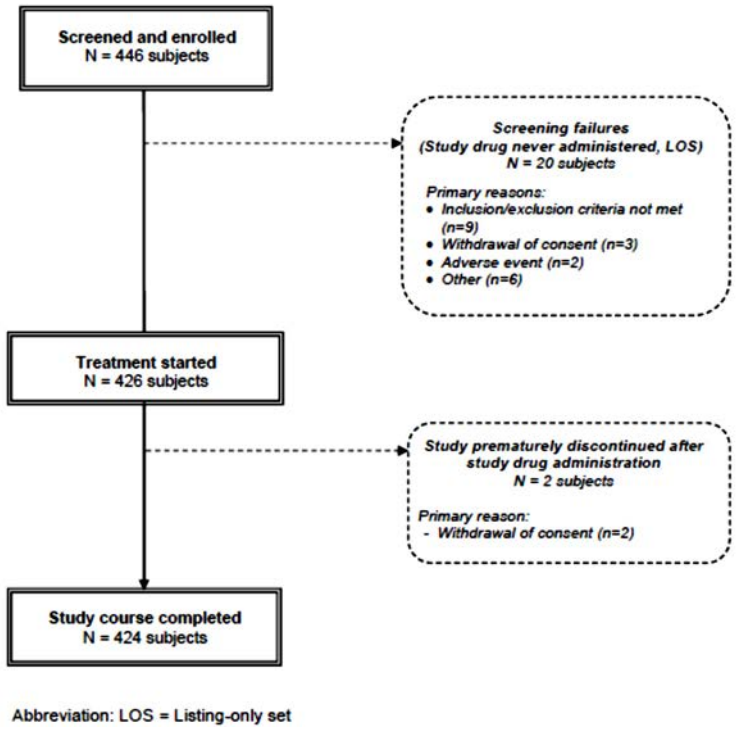
*6.1.1.2.8. Statistical methods*

Statistical analyses were performed using SAS 9.2 or later. Efficacy data were analysed using the FAS with additional sensitivity analyses using the PPS. All statistical tests were 2-sided at the 0.05 significance level with 2-sided 95% CIs based on the McNemar test. Sensitivity and specificity were defined as TP/(TP+FN) and TN/(TN+FP), respectively ( TP = true positive, TN = true negative, FP = false positive and FN = false negative). The evaluation was based on the derived majority response of the three readers. For continuous variables, the arithmetic mean of the responses from the three readers was used. Separate analyses were performed for data from the investigators and each of the blinded readers. The primary efficacy variable and key safety variables were analysed by country, age and race (all patients were female). No imputations were made for efficacy or safety assessments, and uninterpretable images were excluded from the evaluations.

*6.1.1.2.9. Participant flow*

As shown in Figure 3, 446 patients were screened, 426 patients were treated and included in the safety analysis set (SAF), and 424 patients completed the study. There were 20 screening failures and two patients withdrew prematurely.

**Figure 3: Participant flow**




Abbreviation: LOS = Listing-only set

*6.1.1.2.10. Major protocol violations/deviations*

Protocol deviations were recorded in 338 (79.3%) of the 426 patients who received GAD. Major protocol deviations were identified in 82 (19.2%) patients. These included procedure deviations in 10.6% of patients (most commonly related to post-contrast images); inclusion/exclusion errors in 8.5% of patients; and treatment deviations in 3.3% of patients. In the SAF, 96.7% of patients received GAD within ± 10% of the prescribed dose. Ten patients

(2.3%) received doses 10% more than the prescribed dose and one patient received less than 90%.

*6.1.1.2.11. Baseline data*

There were no meaningful differences between the analysis sets. In the SAF, all patients were female with recently diagnosed breast cancer. Most patients were recruited in Germany and S. Korea. The majority were White (75.1%) and 24.2% were Asian. The mean age was 55.5 years, mean body weight was 68.8 kg, mean BMI was 25.9 kg/m$^2$, and the mean eGFR was 91.6 ml/min/1.73m$^2$ (range 54-180). The distribution of malignancies in each of the five breast regions (as illustrated in Figure 2 above) is shown in Table 7. Most patients had a medical (84.3%) and surgical history (69.0%).

**Table 7: Study 91743 Referral diagnosis**

| | Presence of malignancy | |
|---|---|---|
| | Right breast | Left breast |
| **Region 1** | 69 (16.2%) | 75 (17.6%) |
| **Region 2** | 116 (27.2%) | 126 (29.6%) |
| **Region 3** | 49 (11.5%) | 46 (10.8%) |
| **Region 4** | 30 ( 7.0%) | 35 ( 8.2%) |
| **Region 5** | 16 ( 3.8%) | 28 ( 6.6%) |

*6.1.1.2.12. Results for the primary efficacy outcome*

A summary of the within-patient sensitivity for the detection of malignancy for CMRM and UMRM in the FAS is shown in Table 8.

**Table 8: Study 91743 Comparison of within patient sensitivity for detection of malignant disease of CMRM versus UMRM by reader (FAS)**

| | Point estimates (%) | | | 95% confidence interval | |
|---|---|---|---|---|---|
| Reader | CMRM | UMRM | Difference | Lower bound | Upper bound |
| 1 | 83.2 | 36.6 | 46.6 | 41.9 | 51.4 |
| 2 | 79.9 | 49.1 | 30.8 | 25.7 | 35.9 |
| 3 | 86.7 | 63.4 | 23.3 | 19.2 | 27.3 |
| Investigator | 93.8 | 75.9 | 17.8 | 14.2 | 21.4 |

The analyses were based on 388 patients in the FAS.

For each patient the proportion of malignant breast regions that were recognised as malignant using either CMRM or UMRM was determined and the means were calculated across all patients. Superiority of within-patient sensitivity of CMRM over UMRM was demonstrated independent of the blinded reader. With CMRM, within-patient sensitivities were 83.2%, 79.9% and 86.7% for the three blinded readers while the corresponding values for UMRM were 36.6%, 49.1% and 63.4%. The differences in favour of CMRM ranged from 23.3% to 46.6% for the blinded readers compared with 17.8% for the investigator. The null hypothesis was excluded as the lower bound of the 95% CI was larger than zero for each reader. The results of the PPS were similar with differences in favour of CMRM ranging from 23.7% to 48.4%. The specificity of CMRM on a breast level based on non-malignant breasts was greater than the pre-defined 80% threshold. As shown in Table 9, the lower bound of the 95% CI was >80% for all blinded readers in the FAS.

**Table 9: Study 91743 Breast level specificity of CMRM for non-malignant breast by reader (FAS)**

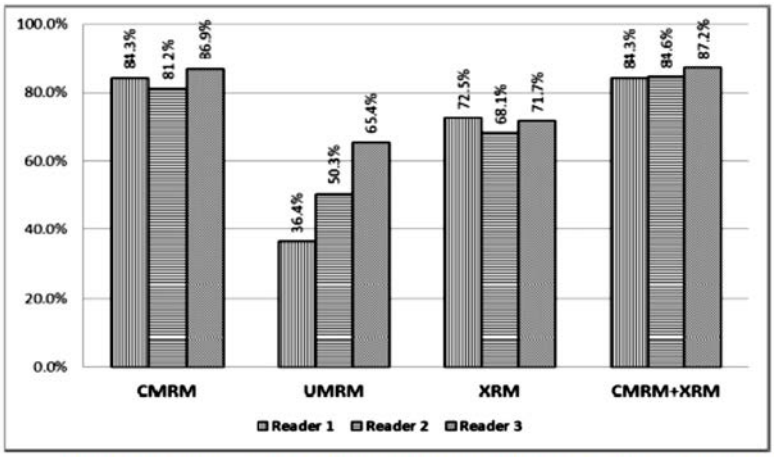
| Reader | Point estimate (%) CMRM | 95% confidence interval Lower bound | Upper bound |
|---|---|---|---|
| 1 | 85.6 | 82.0 | 89.2 |
| 2 | 95.0 | 92.8 | 97.2 |
| 3 | 88.6 | 85.3 | 91.8 |
| Investigator | 95.4 | 93.3 | 97.6 |

The analyses were based on 372 patients; evaluable for specificity were breasts without malignant disease as verified by SoT for which a CMRM assessment was available.

*6.1.1.2.13. Results for other efficacy outcomes*

In the FAS, breast-level specificity based on malignant breasts was greater than the pre-defined threshold of 50% for the three blinded readers with lower bounds for the 95% CI of 58.5%, 59.4% and 61.1%. Index cancers were defined as the regions confirmed as malignant by histology upon enrolment into the study. The proportions of patients with detected index cancers are shown in Figure 4 and Table 10.

**Figure 4: Study 91743 Patient level detection of index cancer by imaging modality and by reader (FAS)**




Note: The analyses were based on 382 patients; index cancer was defined as the cancer confirmed by histology prior to inclusion which made the patient eligible for the study.

**Table 10: Study 91743 Patient level detection of index cancer by imaging modality and by reader (FAS)**

| Imaging method | Reader | Proportion of patients whose index cancers were detected (%) | 95% confidence interval Lower bound | Upper bound |
|---|---|---|---|---|
| UMRM | 1 | 36.4 | 31.6 | 41.4 |
| | 2 | 50.3 | 45.1 | 55.4 |
| | 3 | 65.4 | 60.4 | 70.2 |
| | Investigator | 82.5 | 78.3 | 86.1 |
| CMRM | 1 | 84.3 | 80.2 | 87.8 |
| | 2 | 81.2 | 76.9 | 85.0 |
| | 3 | 86.9 | 83.1 | 90.1 |
| | Investigator | 99.7 | 98.6 | 100.0 |
| XRM | 1 | 72.5 | 67.7 | 76.9 |
| | 2 | 68.1 | 63.1 | 72.7 |
| | 3 | 71.7 | 66.9 | 76.2 |
| | Investigator | 98.4 | 96.6 | 99.4 |
| UMRM+XRM | 1 | 71.5 | 66.7 | 75.9 |
| | 2 | 76.2 | 71.6 | 80.4 |
| | 3 | 77.5 | 73.0 | 81.6 |
| | Investigator | 99.0 | 97.3 | 99.7 |
| CMRM+XRM | 1 | 84.3 | 80.2 | 87.8 |
| | 2 | 84.6 | 80.5 | 88.0 |
| | 3 | 87.2 | 83.4 | 90.4 |
| | Investigator | 100.0 | 99.0 | 100.0 |

The analyses were based on 382 patients (100%); index cancer was defined as the cancer confirmed by histology prior to inclusion which made the patient eligible for the study.

The best detection rates were obtained for CMRM (81.2%, 84.3% and 86.9%) and CMRM + XRM (84.3%, 84.6% and 87.2%) compared with UMRM only (68.1%, 71.7% and 72.5%). The differences in favour of CMRM compared to UMRM were 21.5%, 30.9% and 47.9% for the three readers. The differences were statistically significant as the 95% CI for the comparisons excluded zero for all three blinded readers. Additional cancers were defined as cancers not detected at screening but detected subsequently according to SoT. The numbers and proportions of patients with at least one additional cancer detected by imaging modality are shown in Table 11. The best detection rates were obtained with CMRM (63.2%, 56.3% and 65.5%) and CMRM + XRM (65.5%, 56.3% and 65.5%) compared with UMRM (20.7%, 31.0% and 27.6%). The differences in favour of CMRM compared with UMRM ranged from 25.3% to 42.5%. The differences were statistically significant as the lower bound of the 95% CI excluded zero for each reader.

**Table 11: Study 91743 Patient level detection of additional cancer by imaging modality and by reader (FAS)**

| Imaging method | Reader | Patients where at least one additional cancer was detected | | 95% confidence interval | |
|---|---|---|---|---|---|
| | | n | Proportion (%) | Lower bound | Upper bound |
| UMRM | 1 | 18 | 20.7 | 12.7 | 30.7 |
| | 2 | 27 | 31.0 | 21.5 | 41.9 |
| | 3 | 24 | 27.6 | 18.5 | 38.2 |
| | Investigator | 25 | 28.7 | 19.5 | 39.4 |
| CMRM | 1 | 55 | 63.2 | 52.2 | 73.3 |
| | 2 | 49 | 56.3 | 45.3 | 66.9 |
| | 3 | 57 | 65.5 | 54.6 | 75.4 |
| | Investigator | 52 | 59.8 | 48.7 | 70.1 |
| XRM | 1 | 23 | 26.4 | 17.6 | 37.0 |
| | 2 | 23 | 26.4 | 17.6 | 37.0 |
| | 3 | 30 | 34.5 | 24.6 | 45.4 |
| | Investigator | 9 | 10.3 | 4.8 | 18.7 |
| UMRM+XRM | 1 | 29 | 33.3 | 23.6 | 44.3 |
| | 2 | 37 | 42.5 | 32.0 | 53.6 |
| | 3 | 28 | 32.2 | 22.6 | 43.1 |
| | Investigator | 27 | 31.0 | 21.5 | 41.9 |
| CMRM+XRM | 1 | 57 | 65.5 | 54.6 | 75.4 |
| | 2 | 49 | 56.3 | 45.3 | 66.9 |
| | 3 | 57 | 65.5 | 54.6 | 75.4 |
| | Investigator | 52 | 59.8 | 48.7 | 70.1 |

The analyses were based on 87 patients (100%); additional cancer was defined as cancer which was present according to SoT, but which was not defined as index cancer.

The sensitivity and specificity rates for the detection of malignant disease were shown. Sensitivity was based on 643 breast regions with malignant disease verified by the SoT. Sensitivity rates were consistently higher with CMRM compared with UMRM and the results were statistically significant as the 95% CI excluded zero. For the detection of malignant disease, there was a significant improvement in sensitivity for CMRM compared with UMRM ranging from 25.2% to 44.3% for the three readers. Improved sensitivity rates were also seen for CMRM + XRM compared with XRM (ranging from 15.6% to 18.5%), and for CMRM + XRM compared with UMRM + XRM (ranging from 9.3% to 15.1%). For sensitivity, the median reader value was 83.2% compared with 49.1% for UMRM. Sensitivity for the detection of unifocal disease was 24.7% greater for CMRM compared with UMRM, and 31.3% greater for multifocal disease. The specificity to exclude the presence of malignant disease was based on 3240 breast regions with no disease. Specificity for CMRM compared with UMRM was -6.5%; -4.9% for CMRM + XRM compared with UMRM + XRM; and -4.3% for CMRM + XRM compared with XRM. Using CMRM or CMRM + XRM, specificity to rule out unifocal disease was 89% compared with 87% for multifocal disease. An overview of the key primary and secondary efficacy results for the comparison of CMRM versus UMRM is shown in Table 12 and Table 13.

**Table 12: Study 91743 Overview of efficacy results for CMRM versus UMRM on a patient level by reader (FAS)**

| Analyses | Reader | CMRM | UMRM | Lower bound of 95% CI for the difference CMRM-UMRM > 0 | Superiority of CMRM |
|---|---|---|---|---|---|
| **Co-primary analyses (supplemental SAP)** | | | | | |
| Within-patient sensitivity for detection of | 1 | 83.2 | 36.6 | 41.9 | Yes |
| malignant disease (point estimate, %) | 2 | 79.9 | 49.1 | 25.7 | Yes |
| (N = 388 patients) | 3 | 86.7 | 63.4 | 19.2 | Yes |
| **Secondary analyses (supplemental SAP)** | | | | | |
| Proportion of patients whose index cancers | 1 | 84.3 | 36.4 | 42.3 | Yes |
| were detected (%) | 2 | 81.2 | 50.3 | 24.9 | Yes |
| (N = 382 patients) | 3 | 86.9 | 65.4 | 16.6 | Yes |
| Proportion of patients where at least one | 1 | 63.2 | 20.7 | 30.1 | Yes |
| additional cancer was detected (%) | 2 | 56.3 | 31.0 | 13.0 | Yes |
| (N = 87 patients) | 3 | 65.5 | 27.6 | 24.8 | Yes |

Abbreviation: 95% CI = 95% confidence interval
**Note**: Superiority was indicated when the lower bound of the 95% CI for the difference CMRM - UMRM was above zero.

**Table 13: Study 91743 Overview of efficacy results for CMRM on breast level specificity by reader (FAS)**

| Analyses | Reader | Point estimate CMRM (%) | Lower bound of 95% CI | Performance threshold | Performance threshold met |
|---|---|---|---|---|---|
| **Co-primary analyses (supplemental SAP)** | | | | | |
| Breast level specificity for non-malignant | 1 | 85.6 | 82.0 | > 80% | Yes |
| breasts (point estimate, %) | 2 | 95.0 | 92.8 | > 80% | Yes |
| (N = 372 patients) | 3 | 88.6 | 85.3 | > 80% | Yes |
| **Secondary analyses (supplemental SAP)** | | | | | |
| Breast level specificity for malignant breasts | 1 | 61.1 | 56.3 | > 50% | Yes |
| (point estimate, %) | 2 | 59.4 | 54.5 | > 50% | Yes |
| (N = 388 patients) | 3 | 58.5 | 53.6 | > 50% | Yes |

Abbreviation: 95% CI = 95% confidence interval
**Note**: Above, number of patients are provided. As most patients contributed with one normal and one diseased breast, differences to number of breasts are negligible.

Values following the investigators' assessments were generally higher than the corresponding results of the blinded readers as the investigators had more access to clinical information. Subgroup analyses based on country, age and race showed no significant differences when compared with the overall population.

> **Comment:** The study was well designed and conducted and all reasonable efforts were made to exclude inter-reader variability and bias. The main objective was to compare GAD enhancement with UMRM in malignant breast disease and no positive control arm was included (i.e. another contrast agent). CMRM was significantly superior to UMRM for the detection of malignant breast disease with a 34.1% greater median sensitivity. CMRM also had greater sensitivity than XRM (83.2% versus 70.6%). Performance thresholds for specificity of >80% and >50% were also met for breasts without and without malignancies, respectively. CMRM was also more effective in the detection of index cancers and previously undetected additional cancers.

#### *6.1.1.3. Study 91782 (GEMMA-2)*

##### *6.1.1.3.1. Study design, objectives, locations and dates*

This was a Phase III, multi-centre, open-label, non-randomised study with blinded image evaluations. The study protocol was identical to study 91743 evaluated above. It was conducted at 39 centres in 8 countries (Argentina, Canada, Germany, India, Poland, Spain, Taiwan and the USA) and it completed in March 2012. It was designed to demonstrate superiority of the within-patient sensitivity of combined unenhanced and GAD-enhanced MRM (CMRM) over unenhanced

MRM (UMRM). It was also designed to demonstrate the specificity of CMRM in the detection of malignant versus non-malignant breast lesions. It was planned to enrol at least 440 patients with up to 60 patients at each centre. Patients with recently diagnosed histologically confirmed breast cancer after XRM were referred for breast MRI prior to breast surgery. Breast MRIs were performed using modern 1.5T scanners with dedicated breast coils to enable bilateral breast imaging. Patients received an unenhanced breast MRI, followed by a GAD-enhanced MRI. Unenhanced MRIs (consisting of T2- and T1-weighted 3D spoiled gradient echo pulse sequence) were performed, followed by GAD-enhanced scans (5 acquisitions of T1-weighted 3D spoiled gradient echo pulse sequence with acquisition time ~60 sec).

The patients stayed at the study centre for at least one hour after the MRM examination before being discharged. After 24 hours, the patients returned to the centre for a safety review. Ultrasound examinations were scheduled for patients assessed as disease free as soon as possible after the study MRM, and before any further follow-up and subsequent breast biopsy or surgery. The study ended with the 24 hour follow-up with patients not scheduled for ultrasound investigation, and after the ultrasound investigation for patients who received them.

UMRM, CMRM and XRM image sets were evaluated in a randomised fashion by three independent blinded readers. After evaluation of UMRM, the data were locked and evaluation of the respective XRM was performed together with UMRM. Evaluation of CMRM was then performed, followed by data lock and evaluation of CMRM and XRM. For all examinations, the evaluation of the left and right breasts were performed by regions (5 regions in each breast: 4 quadrants and the central region including nipple) as described previously. For each breast region, an assessment of the presence or absence of malignancy was made. If suspected malignancy was detected, an assessment of whether it was unifocal or multifocal was made. The definition of disease status was assessed using the ACR BI-RADS lexicon for interpretation of MRM and XRM examinations. All suspect lesions detected by MRI were required to be verified histologically. Otherwise, each breast region was assessed as disease free, either with no pathology or with a benign lesion. For regions evaluated as non-diseased without a histological confirmation, additional ultrasound evaluation was performed to confirm the MRM findings. Suspicious ultrasound findings were required to be verified histologically. The standard of truth (SoT) for the diagnostic performance of GAD-enhanced MRM was the final consensus assessment by an independent committee of two experienced breast cancer physicians who were not affiliated with the study.

*6.1.1.3.2. Inclusion and exclusion criteria*

The key inclusion criteria were: female or male patients of any ethnicity aged at least 18 years; recent histologically proven breast cancer identified after XRM of both breasts (according to ACR and performed no longer than 6 weeks prior to enrolment); and eGFR ≥60 ml/min/1.73m$^2$. The key exclusion criteria were pregnant or lactating females; any recent other investigational products; contra-indications to MRM; a history of severe allergic or anaphylactic reactions; any contrast agent within the previous 24 hours; clinically unstable; severe cardiovascular disease; acute or chronic renal impairment; chemotherapy or hormonal therapy for breast cancer within the previous 6 months; hormone replacement therapy within 4 weeks before study drug administration; scheduled or likely to require surgery and/or biopsy within 24 hours of study drug administration; and prior excisional biopsy or breast surgery in the 6 months before enrolment and between XRM and study MRM.

*6.1.1.3.3. Study treatments*

All patients received the same treatment, a single dose of gadobutrol 0.1 mmol/kg BW given via an intravenous catheter.

*6.1.1.3.4. Efficacy variables and outcomes*

The main efficacy variables were defined by matching the readers' assessments for each breast region (by imaging modality) to the corresponding SoT assessment. For each region there were

three choices: no malignant disease, unifocal malignant disease, or multifocal malignant disease present. The value of the primary efficacy variable was determined for each breast region by whether or not the category chosen by the imaging modality matched the disease state determined to be correct by the SoT.

The co-primary efficacy outcomes were (1) to demonstrate the superiority of within-patient sensitivity of combined unenhanced and GAD-enhanced MRM (CMRM) over unenhanced MRM (UMRM), and (2) to demonstrate the breast level specificity of CMRM, based on non-malignant breasts, greater than a performance threshold of 80%.

Other efficacy outcomes included:

- Breast level specificity of CMRM, based on malignant breasts, greater than a performance threshold of 50%.
- Detection of index cancers using CMRM compared with XRM, UMRM, and CMRM + XRM based on a patient level.
- Detection of additional cancer using CMRM compared with XRM, UMRM, and CMRM + XRM based on a patient level.

*6.1.1.3.5. Randomisation and blinding methods*

All patients received the same open-label treatment.

*6.1.1.3.6. Analysis populations*

A total of 460 enrolled patients was planned. Efficacy evaluations were performed using the FAS and PPS. Patients were included in the FAS if they had a valid SoT for at least one variable breast region as well as UMRM and CMRM evaluated by three independent blinded readers. Patients were excluded if the XRM was not available. The PPS included those patients who also fulfilled all major protocol requirements. Patients were excluded from the PPS for violation of inclusion/exclusion criteria; a GAD dose <90% or >110% of the required dose; MRM procedure errors; or invalid SoT procedures. The safety analysis set (SAF) consisted of all patients who received any dosage of GAD. A total of 460 patients were screened of whom 439 patients were treated and included in the SAF. A total of 397 (86.3%) patients were included in the FAS and 351 (76.3%) patients were included in the PPS.

*6.1.1.3.7. Sample size*

The sample size was amended based on the results of study 91743 (GEMMA-1). The results suggested a difference of 0.3 between CMRM and UMRM for within-patient sensitivity with a 40% proportion of discordant pairs for a single reader. With this assumption, 44 independent breast regions were needed for 90% power. The results also suggested a breast level specificity of 0.87 in CMRM for a single reader. With these assumptions, 299 patients with at least one non-malignant breast were required to achieve 90% power. Thus, the overall power of the study was expected to be 90% or more.

*6.1.1.3.8. Statistical methods*

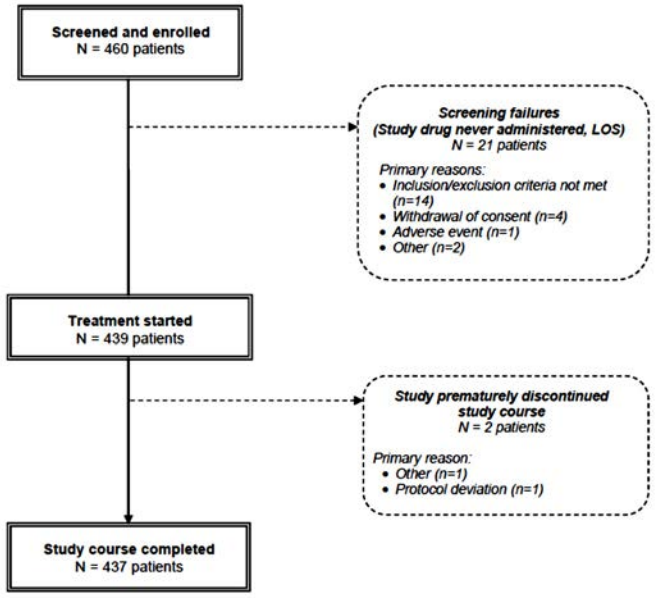
Statistical analyses were performed using SAS 9.2 or higher. Efficacy data were analysed using the FAS with additional sensitivity analyses using the PPS. All statistical tests were 2-sided at the 0.05 significance level with 2-sided 95% CIs based on the McNemar test. Sensitivity and specificity were defined as TP/(TP+FN) and TN/(TN+FP), respectively (TP = true positive, TN = true negative, FP = false positive and FN = false negative). The evaluation was based on the derived majority response of the three readers. For continuous variables, the arithmetic mean of the responses from the three readers was used. Separate analyses were performed for data from the investigators and each of the blinded readers. The primary efficacy variable and key safety variables were analysed by country, age and race (all but one patient was female). No

imputations were made for efficacy or safety assessments, and uninterpretable images were excluded from the evaluations.

*6.1.1.3.9. Participant flow*

The disposition of patients is shown below in Figure 5, below. A total of 460 patients were enrolled, 439 patients were treated and 437 patients completed the study.

**Figure 5: Patient disposition**




Abbreviation: LOS = Listing-only set

*6.1.1.3.10. Major protocol violations/deviations*

Minor protocol deviations were recorded for 78.1% of patients in the SAF. Major protocol deviations were identified in 70 (15.9%) patients: procedure deviations in 9.6%, inclusion/exclusion errors in 4.8%, and treatment deviations in 4.3%. In the FAS, 97.0% received GAD within ± 10% of the prescribed dose. Two patients (0.5%) received less than 90% of the prescribed dose and nine patients (2.3%) received doses greater than 10% above the prescribed dose.

*6.1.1.3.11. Baseline data*

Baseline demographic data for the SAF, FAS and PPS showed no meaningful differences between the analysis sets. In the SAF, all but one patient were female with recently diagnosed breast cancer. The majority of patients were White (70.6%) and 23.7% were Asian. The mean age was 57.1 years, mean body weight was 69.0 kg, mean BMI was 26.8 kg/m$^2$, and mean eGFR was 91.8 ml/min/1.73m$^2$ (range 33-160). The distribution of malignancies in each of the five breast regions is shown in Table 14. Most patients had a medical (82.7%) and surgical history (44.0%).

**Table 14: Study 91782 Referral diagnosis**

| | Presence of malignancy | |
|---|---|---|
| | Right breast | Left breast |
| Region 1 | 48 (10.9%) | 78 (17.8%) |
| Region 2 | 121 (27.6%) | 146 (33.3%) |
| Region 3 | 43 ( 9.8%) | 39 ( 8.9%) |
| Region 4 | 33 ( 7.5%) | 25 ( 5.7%) |
| Region 5 | 21 ( 4.8%) | 29 ( 6.6%) |

Each analysis was based on a total number of each region of 439 (= 100%).

*6.1.1.3.12. Results for the primary efficacy outcome*

A summary of the within-patient sensitivity for the detection of malignancy for CMRM and UMRM in the FAS was shown. For each patient the proportions of malignant breast regions that were recognised as malignant using either CMRM or UMRM was determined: the means were then calculated across all patients. Superiority of within-patient sensitivity of CMRM over UMRM was demonstrated independent of the blinded reader. With CMRM, within-patient sensitivities were 88.6%, 89.0% and 85.5% for the three blinded readers while the corresponding values for UMRM were 73.3%, 57.0% and 55.1%. The differences in favour of CMRM ranged from 15.2% to 25.8%. The null hypothesis was excluded as the lower bound of the 95% CI was larger than zero for each reader. The results of the PPS were similar with differences in favour of CMRM ranging from 14.7% to 30.8%. The mean specificity of CMRM on a breast level based on non-malignant breasts was greater than the pre-defined 80% threshold. However, as shown in Table 15, the lower bound of the 95% CI was >80% for only 2/3 of the blinded readers. In the FAS, the lower bounds of the 95% CI were 89.1%, 80.2% and 79.0% for the three readers. In the PPS, the corresponding values were 88.4%, 79.4% and 78.9%.

**Table 15: Study 91782 Breast level specificity of CMRM for non-malignant breasts by reader (FAS)**

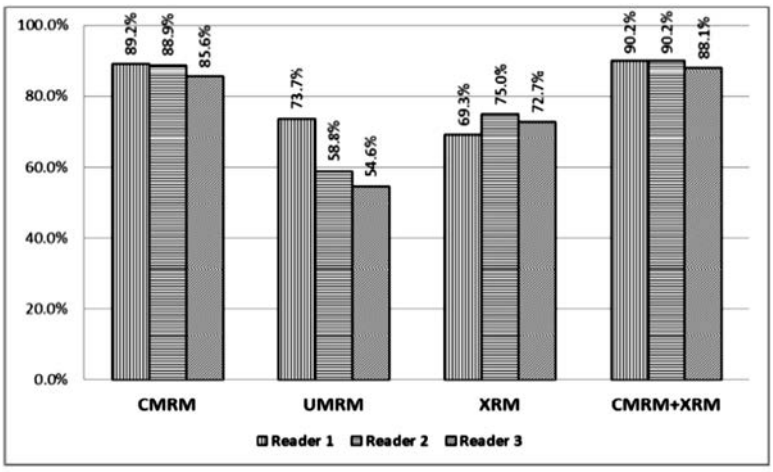
| Reader | Point estimate (%) CMRM | 95% confidence interval Lower bound | Upper bound |
|---|---|---|---|
| 1 | 91.8 | 89.1 | 94.6 |
| 2 | 83.9 | 80.2 | 87.7 |
| 3 | 82.8 | 79.0 | 86.7 |
| Investigator | 95.4 | 93.3 | 97.5 |

The analyses were based on 367 patients; evaluable for specificity were breasts without malignant disease as verified by SoT for which a CMRM assessment was available.

*6.1.1.3.13. Results for other efficacy outcomes*

In the FAS, breast-level specificity based on malignant breasts was greater than the pre-defined threshold of 50% for only 1/3 readers. The lower bounds for the 95% CI for the three blinded readers were 49.9%, 42.2% and 50.6%. Index cancers were defined as the regions confirmed as malignant by histology upon enrolment into the study. The proportions of patients with detected index cancers are shown in Figure 6 and Table 16.

**Figure 6: Study 91782 Patient level detection of index cancer by imaging modality and by reader (FAS)**




Note: The analyses were based on 388 patients (100%); index cancer was defined as the cancer confirmed by histology prior to inclusion which made the patient eligible for the study.

**Table 16: Study 91782 Patient level detection of index cancer by imaging modality and by reader (FAS)**

| Imaging method | Reader | Proportion of patients whose index cancers were detected (%) | 95% confidence interval Lower bound | Upper bound |
|---|---|---|---|---|
| UMRM | 1 | 73.7 | 69.0 | 78.0 |
| | 2 | 58.8 | 53.7 | 63.7 |
| | 3 | 54.6 | 49.5 | 59.7 |
| | Investigator | 84.8 | 80.8 | 88.2 |
| CMRM | 1 | 89.2 | 85.7 | 92.1 |
| | 2 | 88.9 | 85.4 | 91.9 |
| | 3 | 85.6 | 81.7 | 88.9 |
| | Investigator | 99.0 | 97.4 | 99.7 |
| XRM | 1 | 69.3 | 64.5 | 73.9 |
| | 2 | 75.0 | 70.4 | 79.2 |
| | 3 | 72.7 | 68.0 | 77.1 |
| | Investigator | 96.6 | 94.3 | 98.2 |
| UMRM+XRM | 1 | 82.7 | 78.6 | 86.4 |
| | 2 | 83.0 | 78.9 | 86.6 |
| | 3 | 80.9 | 76.7 | 84.7 |
| | Investigator | 98.2 | 96.3 | 99.3 |
| CMRM+XRM | 1 | 90.2 | 86.8 | 93.0 |
| | 2 | 90.2 | 86.8 | 93.0 |
| | 3 | 88.1 | 84.5 | 91.2 |
| | Investigator | 99.5 | 98.2 | 99.9 |

The analyses were based on 388 patients (100%); index cancer was defined as the cancer confirmed by histology prior to inclusion which made the patient eligible for the study.

The best detection rates were obtained for CMRM (89.2%, 88.9% and 85.6%) and CMRM + XRM (90.2%, 90.2% and 88.1%) compared with UMRM only (73.7%, 58.8% and 54.6%). The differences in favour of CMRM compared to UMRM were 15.5%%, 30.2% and 30.9% for the three readers. The differences were statistically significant as the 95% CI for the comparisons excluded zero for all three blinded readers. Additional cancers were defined as cancers not detected at screening but detected subsequently according to SoT. The numbers and proportions of patients with at least one additional cancer detected by imaging modality were shown. The best detection rates were obtained with CMRM (69.0%, 78.6% and 56.8%) and CMRM + XRM (69.0%, 78.6% and 70.2%) compared with UMRM (45.2%, 34.5% and 33.3%). The differences in favour of CMRM compared with UMRM ranged from 23.8% to 48.8%. The differences were statistically significant as the lower bound of the 95% CI excluded zero for each reader.

The sensitivity and specificity rates for the detection of malignant disease (unifocal and multifocal) were shown. Sensitivity was based on 630 breast regions with malignant disease verified by the SoT. Sensitivity rates were consistently higher with CMRM compared with UMRM and the results were statistically significant as the 95% CI excluded zero. For the detection of malignant disease, there was a significant improvement in sensitivity for CMRM compared with UMRM ranging from 17.5% to 32.1% for the three readers. Improved sensitivity rates were also seen for CMRM + XRM compared with XRM (ranging from 16.5% to 24.3%), and for CMRM + XRM compared with UMRM + XRM (ranging from 9.5% to 12.5%).

Sensitivity for the detection of unifocal disease was based on 570 regions with SoT confirmed unifocal malignancy. Compared with UMRM, CMRM sensitivity was improved for 2/3 blinded readers by 4.6% and 19.5%, and reduced by -5.8% for 1/3 readers. A benefit in favour of CMRM was statistically significant for only one reader. Sensitivity for multifocal malignant disease was based on 60 breast regions. There was a statistically significant benefit in favour of CMRM for all readers by 46.7%, 51.7% and 31.7%. The specificity to exclude the presence of unifocal and multifocal malignant disease was based on 3257 and 3767 breast regions with no disease, respectively. The specificity for CMRM compared with UMRM ranged from -3.2% to -7.3% for unifocal disease, and from -2.3% to -6.5% for multifocal disease. None of the differences was statistically significant for any reader. Differences in sensitivity for CMRM + XRM compared with UMRM + XRM ranged from 9.5% to 12.5%; and from 16.5% to 24.3% for CMRM + XRM

compared with XRM. The differences were statistically significant for all readers. There were no specificity benefits in favour of CMRM for any imaging modalities.

Values following the investigators' assessments were generally higher than the corresponding results of the blinded readers as the investigators had more access to clinical information. Improvements in sensitivity by CMRM versus UMRM were 19% to detect malignant breast disease, 12.0% to detect unifocal malignant disease, and 25.4% to detect multifocal malignant disease. The differences were statistically significant in each case. Sensitivity subgroup analyses based on country, age and race showed no significant differences when compared with the overall population.

> **Comment:** The results of this study confirmed GEMMA-1 although the results were less consistent. For the first co-primary endpoint, the within-patient sensitivity of CMRM to detect malignant disease was superior to UMRM. The differences ranging from 15.2% to 31.9% in favour of CMRM were statistically significant. For the second co-primary endpoint, the breast level specificity of CMRM based on non-malignant breasts met the pre-defined 80% threshold but only for 2/3 blinded readers. The results for the secondary efficacy endpoints were also inconsistent. However, overall sensitivity and specificity rates favoured CMRM compared with UMRM

### 6.1.2. Other efficacy studies

#### *6.1.2.1. Study 94055/99012*

Study 94055 has been evaluated previously. Study 99012 is a *post hoc* analysis of study 94055 to compare the sensitivity, specificity and accuracy of non-enhanced and GAD-enhanced MRI in the detection of malignant versus benign lesions, and exact diagnosis in various body regions. 94055/99012 was a multicentre, non-randomised, open-label, single dose, intra-individually controlled study. Gadovist® 0.1 mmol/kg BW was administered to each patient. There was no active control group and the unenhanced MRI was used as an internal comparator. A total of 180-290 patients was planned with indications for different body regions including liver, bone, soft tissue, pelvic and thoracic organs, and breast lesions. A total of 182 patients was included in the study and 170 patients had an assessable SoT. Of these, 151 patients had both MRIs assessed by all the blinded readers. The statistical evaluation employed descriptive statistics using SAS 9.1. The final diagnosis was based on the SoT using all information available to the investigator including the MRI results. The frequencies of procedures performed to reach the final diagnosis in 137 patients with all images evaluated by all blinded readers are shown in Table 17.

**Table 17: Study 94055/99012 Frequencies of procedures (biopsy/Surgery/Cytology) performed to reach referral/final diagnosis in subjects with all images evaluated by all blinded readers (complete cases)**

| | Baseline | Final Diagnosis | Any Timepoint |
|---|---|---|---|
| n | 137 (100.0%) | 137 (100.0%) | 137 (100.0%) |
| Biopsy performed | | | |
| no | 85 ( 62.0%) | 103 ( 75.2%) | 59 ( 43.1%) |
| yes | 52 ( 38.0%) | 34 ( 24.8%) | 78 ( 56.9%) |
| Surgery performed | | | |
| no | 120 ( 87.6%) | 87 ( 63.5%) | 78 ( 56.9%) |
| yes | 17 ( 12.4%) | 50 ( 36.5%) | 59 ( 43.1%) |
| Cytology performed | | | |
| missing | 79 ( 57.7%) | 79 ( 57.7%) | 79 ( 57.7%) |
| no | 33 ( 24.1%) | 51 ( 37.2%) | 27 ( 19.7%) |
| yes | 25 ( 18.2%) | 7 ( 5.1%) | 31 ( 22.6%) |
| Any of biospy, surgery or cytology performed | | | |
| no | 74 ( 54.0%) | 59 ( 43.1%) | 28 ( 20.4%) |
| yes | 63 ( 46.0%) | 78 ( 56.9%) | 109 ( 79.6%) |

Patients with a non-assessable SoT were excluded from the analysis. Sensitivity, specificity and accuracy were calculated per reader as described Sensitivity and specificity were defined as TP/(TP+FN) and TN/(TN+FP), respectively, categorised in Table 18.

**Table 18: Study 94055/99012**

| | SOT | |
|---|---|---|
| MRI assessment | malignant | benign |
| malignant | true positive (TP) | false positive (FP) |
| benign | false negative (FN) | true negative (TN) |
| not assessable | false negative (FN) | false positive (FP) |

*6.1.2.1.1. Efficacy results*

The primary analysis for sensitivity, specificity and accuracy for malignant lesions was based on the average reader's assessment as shown in Tables 19-21.

**Table 19: Study 94055/99012 Sensitivity of malignant lesion classification (blinded readers) in percent and difference in percentage points for Gadovist enhanced and unenhanced MRI**

| Reader | Number of Subjects | Sensitivity unenhanced MRI | Sensitivity Gadovist enhanced MRI | Difference in Sensitivity | Lower 95% CL for the Difference | CL Upper 95% CL for the Difference |
|---|---|---|---|---|---|---|
| Average Reader | 74 | 72.52 | 80.63 | 8.11 | 4.51 | 11.71 |
| Reader 1 | 78 | 75.64 | 83.33 | 7.69 | -5.51 | 20.89 |
| Reader 2 | 76 | 65.79 | 82.89 | 17.11 | 0.97 | 33.24 |
| Reader 3 | 78 | 74.36 | 76.92 | 2.56 | -9.74 | 14.87 |

**Table 20: Study 94055/99012 Specificity of malignant lesion classification (blinded readers) in percent and difference in percentage points for Gadovist enhanced and unenhanced MRI**

| Reader | Number of Subjects | Specificity unenhanced MRI | Specificity Gadovist enhanced MRI | Difference in Specificity | Lower 95% CL for the Difference | CL Upper 95% CL for the Difference |
|---|---|---|---|---|---|---|
| Average Reader | 63 | 52.91 | 60.85 | 7.94 | 3.52 | 12.35 |
| Reader 1 | 67 | 55.22 | 71.64 | 16.42 | 1.01 | 31.83 |
| Reader 2 | 65 | 44.62 | 49.23 | 4.62 | -14.32 | 23.55 |
| Reader 3 | 66 | 57.58 | 66.67 | 9.09 | -5.49 | 23.67 |

**Table 21: Study 94055/99012 Accuracy of malignant lesion classification (blinded reader) in percent and difference in percentage points for Gadovist enhanced and unenhanced MRI**

| Reader | Number of Subjects | Accuracy unenhanced MRI | Accuracy Gadovist enhanced MRI | Difference in Accuracy | Lower 95% CL for the Difference | CL Upper 95% CL for the Difference |
|---|---|---|---|---|---|---|
| Average Reader | 137 | 63.50 | 71.53 | 8.03 | 4.03 | 12.02 |
| Reader 1 | 145 | 66.21 | 77.93 | 11.72 | 4.68 | 18.77 |
| Reader 2 | 141 | 56.03 | 67.38 | 11.35 | 2.73 | 19.97 |
| Reader 3 | 144 | 66.67 | 72.22 | 5.56 | -1.07 | 12.18 |

All the average assessments were statistically significantly higher for GAD-enhanced MRI compared with unenhanced MRI, although this was not demonstrated by all readers for all assessments. There was a benefit in favour of GAD-enhanced MRI of 8.11% (95% CI: 4.51, 11.71) for sensitivity; 7.94% (95% CI: 3.52, 12.35) for specificity; and 8.03% (95% CI: 4.03, 12.02) for accuracy. Differences in sensitivity, specificity and accuracy of malignant versus benign lesions per body region are shown in Tables 22-24. GAD-enhanced MRI improved the

exact diagnosis, or was no worse, compared with unenhanced MRI both overall and for each body region, on average and for each blinded reader (Table 25).

**Table 22: Study 94055/99012 Sensitivity of malignant lesion classification (blinded readers) in percentage points for Gadovist enhanced and unenhanced MRI by body region**

| Body Region | Reader | Number of Subjects | Sensitivity unenhanced MRI | Sensitivity Gadovist enhanced MRI | Difference in Sensitivity |
|---|---|---|---|---|---|
| bone/soft tissue | Average Reader | 17 | 49.02 | 56.86 | 7.84 |
| | Reader 1 | 18 | 50.00 | 50.00 | 0.00 |
| | Reader 2 | 18 | 61.11 | 72.22 | 11.11 |
| | Reader 3 | 18 | 38.89 | 50.00 | 11.11 |
| liver | Average Reader | 8 | 66.67 | 83.33 | 16.67 |
| | Reader 1 | 9 | 66.67 | 88.89 | 22.22 |
| | Reader 2 | 8 | 50.00 | 87.50 | 37.50 |
| | Reader 3 | 10 | 80.00 | 80.00 | 0.00 |
| pelvic organs | Average Reader | 31 | 63.50 | 71.53 | 8.03 |
| | Reader 1 | 32 | 66.21 | 77.93 | 11.72 |
| | Reader 2 | 32 | 56.03 | 67.38 | 11.35 |
| | Reader 3 | 31 | 66.67 | 72.22 | 5.56 |
| breast | Average Reader | 6 | 11.11 | 55.56 | 44.44 |
| | Reader 1 | 6 | 0.00 | 50.00 | 50.00 |
| | Reader 2 | 6 | 0.00 | 50.00 | 50.00 |
| | Reader 3 | 7 | 42.86 | 71.43 | 28.57 |
| lung | Average Reader | 12 | 100.00 | 100.00 | 0.00 |
| | Reader 1 | 13 | 100.00 | 100.00 | 0.00 |
| | Reader 2 | 12 | 100.00 | 100.00 | 0.00 |
| | Reader 3 | 12 | 100.00 | 100.00 | 0.00 |

**Table 23: Study 94055/99012 Specificity of malignant lesion classification (blinded readers) in percentage points for Gadovist enhanced and unenhanced MRI by body region**

| Body Region | Reader | Number of Subjects | Specificity unenhanced MRI | Specificity Gadovist enhanced MRI | Difference in Specificity |
|---|---|---|---|---|---|
| bone/soft tissue | Average Reader | 34 | 66.67 | 72.55 | 5.88 |
| | Reader 1 | 36 | 63.89 | 77.78 | 13.89 |
| | Reader 2 | 35 | 68.57 | 62.86 | -5.71 |
| | Reader 3 | 36 | 63.89 | 80.56 | 16.67 |
| liver | Average Reader | 20 | 48.33 | 58.33 | 10.00 |
| | Reader 1 | 22 | 63.64 | 68.18 | 4.55 |
| | Reader 2 | 21 | 23.81 | 47.62 | 23.81 |
| | Reader 3 | 21 | 57.14 | 66.67 | 9.52 |
| pelvic organs | Average Reader | 4 | 8.33 | 0.00 | -8.33 |
| | Reader 1 | 4 | 0.00 | 0.00 | 0.00 |
| | Reader 2 | 4 | 0.00 | 0.00 | 0.00 |
| | Reader 3 | 4 | 25.00 | 0.00 | -25.00 |
| breast | Average Reader | 5 | 13.33 | 40.00 | 26.67 |
| | Reader 1 | 5 | 0.00 | 100.00 | 100.00 |
| | Reader 2 | 5 | 0.00 | 0.00 | 0.00 |
| | Reader 3 | 5 | 40.00 | 20.00 | -20.00 |

**Table 24: Study 94055/99012 Accuracy of malignant lesion classification (blinded reader) in percent and difference in percentage points for Gadovist enhanced and unenhanced MRI**

| Body Region | Reader | Number of Subjects | Accuracy unenhanced MRI | Accuracy Gadovist enhanced MRI | Difference in Accuracy |
|---|---|---|---|---|---|
| bone/soft tissue | Average Reader | 51 | 60.78 | 67.32 | 6.54 |
| | Reader 1 | 54 | 59.26 | 68.52 | 9.26 |
| | Reader 2 | 53 | 66.04 | 66.04 | 0.00 |
| | Reader 3 | 54 | 55.56 | 70.37 | 14.81 |
| liver | Average Reader | 28 | 53.57 | 65.48 | 11.90 |
| | Reader 1 | 31 | 64.52 | 74.19 | 9.68 |
| | Reader 2 | 29 | 31.03 | 58.62 | 27.59 |
| | Reader 3 | 31 | 64.52 | 70.97 | 6.45 |
| pelvic organs | Average Reader | 35 | 79.05 | 80.00 | 0.95 |
| | Reader 1 | 36 | 86.11 | 88.89 | 2.78 |
| | Reader 2 | 36 | 63.89 | 77.78 | 13.89 |
| | Reader 3 | 35 | 82.86 | 74.29 | -8.57 |
| breast | Average Reader | 11 | 12.12 | 48.48 | 36.36 |
| | Reader 1 | 11 | 0.00 | 72.73 | 72.73 |
| | Reader 2 | 11 | 0.00 | 27.27 | 27.27 |
| | Reader 3 | 12 | 41.67 | 50.00 | 8.33 |
| lung | Average Reader | 12 | 100.00 | 100.00 | 0.00 |
| | Reader 1 | 13 | 100.00 | 100.00 | 0.00 |
| | Reader 2 | 12 | 100.00 | 100.00 | 0.00 |
| | Reader 3 | 12 | 100.00 | 100.00 | 0.00 |

**Table 25: Study 94055/99012 Overall agreement of exact diagnosis in percent and difference in percentage points for Gadovist enhanced and unenhanced MRI by body region**

| Body Region | Reader | Number of Subjects | Overall Agreement unenhanced MRI | Overall Agreement Gadovist enhanced MRI | Difference in Overall Agreement |
|---|---|---|---|---|---|
| OVERALL | Average Reader | 137 | 35.77 | 43.55 | 7.79 |
| | Reader 1 | 145 | 39.31 | 48.97 | 9.66 |
| | Reader 2 | 141 | 29.08 | 38.30 | 9.22 |
| | Reader 3 | 144 | 38.19 | 45.14 | 6.94 |
| bone/soft tissue | Average Reader | 51 | 26.80 | 32.68 | 5.88 |
| | Reader 1 | 54 | 29.63 | 35.19 | 5.56 |
| | Reader 2 | 53 | 26.42 | 26.42 | 0.00 |
| | Reader 3 | 54 | 24.07 | 37.04 | 12.96 |
| liver | Average Reader | 28 | 38.10 | 48.81 | 10.71 |
| | Reader 1 | 31 | 35.48 | 54.84 | 19.35 |
| | Reader 2 | 29 | 27.59 | 44.83 | 17.24 |
| | Reader 3 | 31 | 51.61 | 54.84 | 3.23 |
| pelvic organs | Average Reader | 35 | 65.71 | 70.48 | 4.76 |
| | Reader 1 | 36 | 75.00 | 80.56 | 5.56 |
| | Reader 2 | 36 | 52.78 | 66.67 | 13.89 |
| | Reader 3 | 35 | 65.71 | 65.71 | 0.00 |
| breast | Average Reader | 11 | 6.06 | 30.30 | 24.24 |
| | Reader 1 | 11 | 0.00 | 27.27 | 27.27 |
| | Reader 2 | 11 | 0.00 | 27.27 | 27.27 |
| | Reader 3 | 12 | 16.67 | 33.33 | 16.67 |
| lung | Average Reader | 12 | 8.33 | 11.11 | 2.78 |
| | Reader 1 | 13 | 23.08 | 23.08 | 0.00 |
| | Reader 2 | 12 | 0.00 | 0.00 | 0.00 |
| | Reader 3 | 12 | 8.33 | 8.33 | 0.00 |

**Comment:** The study results support the proposed claim for whole body imaging. The sensitivity and specificity of GAD CMRM were superior to UMRM for all three readers. The benefit in favour of CMRM was demonstrated for all body regions although no

patients with lung disease were examined. The study was open-label but the readers were blinded. There was no active comparator but GAD proved superior to UMRM with patients acting as their own controls.

#### *6.1.2.2. Literature review – whole body imaging*

The sponsor has submitted a literature review of articles published up to February 2013 based on Gadovist® (GAD) and two leading gadolinium-containing comparators, Magnevist® (MAG) and Dotarem® (DOT).

Inclusion criteria for the review were:

- Intravenous administration for any indication other than those currently approved for GAD in Australia
- At least 10 patients
- Included sensitivity or specificity data, or used CE-MRI as the standard of reference.

Exclusion criteria for the review were:

- Articles published only as abstracts
- Animal studies
- Studies in approved indications in Australia
- Case reports
- Review articles
- Duplicates
- Administration by other than intravenous routes.

Papers that met the inclusion/exclusion criteria were then selected for analysis if the following additional criteria were met:

- The patient population was representative of the population likely to receive GAD in normal clinical practice.
- The reference standard was likely to classify the target condition correctly.
- The time period between the reference standard and the index test was short enough to exclude changes in the target condition between tests.
- The index test results were assessed by blinded readers.

Some studies that did not meet all the listed criteria were also included in the review if they were considered notable. These studies related mainly to the thoracic space and cardiac studies. A total of 121 full-length articles for indications not currently approved for GAD were identified. A total of 18 GAD articles satisfied the inclusion criteria but an additional three GAD and one DOT articles with comparative information were reviewed. Of the MAG and DOT articles that met the inclusion criteria, no more than five articles with the largest sample size were selected for review for each anatomic region or organ. After applying this filter, 58 MAG articles and 35 DOT articles were reviewed. The selection of GAD articles was based on specified criteria. A total of 88 articles were rejected because there was no evaluation of sensitivity and specificity. Similar flow charts for the selection of MAG and DOT articles were shown.

The majority of articles assessed the heart (13) and most were perfusion studies. Other body areas assessed breast (2), prostate (2) and uterus (1). Body areas included in the MAG and DOT reviews were shown. All relevant body areas were represented in one or other review as shown in Table 26.

### Table 26: Literature review. Evaluable studies

Evaluable studies selected from the literature review for inclusion in this submission, that reported sensitivity and specificity, comprised:

- Head and Neck region: 5 studies with Magnevist and 3 with Dotarem.
- Thoracic space: 5 studies with Magnevist and 2 with Dotarem.
- Breast: 2 studies with Gadovist, 5 with Magnevist and 5 with Dotarem.
- Abdomen (pancreas, spleen and gallbladder): 5 studies with Magnevist and 1 study with Dotarem.
- Other abdominal regions (colon, small intestine): 5 studies with Magnevist and 2 with Dotarem.
- Pelvis (male, prostate): 2 studies with Gadovist, 5 studies with Magnevist and 5 with Dotarem.
- Pelvis (bladder): 4 studies with Magnevist.
- Pelvis (female, uterus and cervix): 1 study with Gadovist, 5 with Magnevist and 5 with Dotarem.
- Extremities and musculo-skeletal system: 5 studies with Magnevist and 4 with Dotarem.
- Heart (cardiac perfusion imaging): 8 studies with Gadovist, 5 with Magnevist and 2 with Dotarem.
- Heart (delayed enhancement): 5 studies with Gadovist, 5 with Magnevist and 6 with Dotarem.

*6.1.2.2.1.* Head and neck region: *No publications for GAD were found. The five largest MAG publications were identified and all studies showed good diagnostic accuracy with contrast-enhanced images (Table 27).*

### Table 27: Literature Review Magnevist-Diagnostic efficacy in imaging of the head and neck

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease or number of lesions | Patients without disease or samples without lesion | | | | |
| King et al. 2006 [58] | 77 | 7[a] | 70 | 100 | 95 | 43 | 100 |
| Jeon et al. 2008 [50] | 158 | 30[b] | 128 | 100 | 87 | 64 | 100 |
| Ng et al. 2011 [82] | 79 | 29[e] | 50 | 55.2 | 90 | 76.2 | 77.6 |
| Yabuuchi et al. 2008 [129] | 50[c] | 14 | 36 | 71 | 86 | 67 | 89 |
| Sumi et al. 2007 [108] | 67[d] | 34[d] | 33[d] | 83 | 89 | 89 | 84 |

[a] Nasopharyngeal carcinoma
[b] Inverted papilloma. All patients had known lesions.
[c] Tumor characterisation (malignant vs. benign) in parotid gland tumors. 50 tumors in 47 patients.
[d] 34 metastatic and 33 reactive lymph nodes less than 10 mm in diameter were evaluated in 38 patients with squamous cell carcinoma
[e] Oropharyngeal or hypopharyngeal carcinoma
PPV: Positive predictive value, NPV: Negative predictive value

Diagnoses evaluated in the studies were nasopharyngeal carcinoma (King, 2006), benign nasal papilloma (Jeon, 2008), parotid gland tumours (Yabuuchi, 2008), oropharyngeal and hypopharyngeal carcinoma (Ng, 2011) and lymph node involvement in squamous cell carcinoma (Sumi, 2007). Diagnostic efficacy was also demonstrated in two of the three DOT publications found (Dubrulle, 2006; De Foer, 2010; King, 2011) (Table 28).

**Table 28: Literature Review Dotarem Diagnostic efficacy in imaging of the head and neck**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Dubrulle et al. 2006 [28] | 24 | 13 | 11 | 100 | 91 | 93 | 100 |
| De Foer et al. 2010 [23] | 120 | 95 | 25 | 56.7 | 67.6 | 88 | 27 |
| King et al. 2011 [59] | 246 | 77 | 169 | 100 | 93 | 87 | 100 |

PPV: Positive predictive value, NPV: Negative predictive value

Sensitivity ranged from 55.2%-100% for MAG, and from 56.7%-100% for DOT. Specificity ranged from 86%-95% for MAG, and from 67.6%-93% for DOT. The effectiveness of CE-MRI varies with organ and tumour types but it is accepted as one of a range of indispensable imaging tools for the head and neck, including CT, CTA, MRA and PET (Ghandi, 2009).

**Thoracic space:** No GAD studies met all the inclusion criteria. Five MAG studies were selected (Kono, 2007; Schaefer, 2004; Zou, 2008; Tanaka, 2009; Yi, 2008) and two DOT studies met the review criteria (Padovani, 1993; Revel, 2012) (Table 29). Diagnoses evaluated were mainly pulmonary nodules and chest wall invasion and diagnostic efficacy for CE-MRI was demonstrated in all studies. Sensitivity and specificity ranges were 52-100% and 76.9-96%, respectively for MAG, and 78.7-89.6% and 85-100% for DOT. CT remains the initial investigation of choice for imaging of the chest but CE-MRI is indicated when CT findings are equivocal. CE-MRI is superior to CT in some circumstances such as the detection of tumour infiltration of the the chest wall, pleura and mediastinum (Ohno, 2001).

**Table 29: Literature Review Magnevist (top) and Dotarem (bottom) Diagnostic efficacy of thoracic imaging**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Kono et al. 2007 [62] | 171[a] | 144[a] | 27[a] | 94 | 96 | 99 | 74 |
| Schaefer et al. 2004 [97] | 51 | 27[b] | 24 | 100 | 79 | *84* | *100* |
| Zou et al. 2008 [133] | 68 | 52[c] | 13[c] | 98 | 81 | 94 | 93 |
| Tanaka et al. 2009 [110] | 46 | 33[d] | 13 | 97 | 76.9 | *91* | *91* |
| Yi et al. 2008 [130] | 154[e] | 31[e] | 123 | 52 | 94 | 70 | 89 |

[a] Lung cancer vs. benign (hamartoma or tuberculoma); another 31 patients had focal organizing pneumonia, which was analysed separately
[b] Malignant versus benign
[c] Malignant or active inflammatory nodule versus benign. Note: Results shown here were inverted from the original report to allow comparison with other studies. In the original report, the sensitivity for detection of benign lesions was 81%, with a specificity of 98%.
[d] Invasive adenocarcinoma
[e] 154 patients underwent M staging; 31 had confirmed metastatic disease (whole-body)
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.

| Study Module 5.4 | Sample Size | | | | Sensitivity % | Specificity % | PPV % | NPV % |
|---|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | | |
| Padovani et al. 1993 [84] | 33[a] | 20[b] | 13 | | 85 | 85 | *89* | *79* |
| Revel et al. 2012 [93] | 274 | 103[c] | 171 | Rd 1[d] | 84.5<br>89.6 | 99.1<br>97.4 | 98.6<br>95.8 | 89.5<br>93.5 |
| | | | | Rd 2[d] | 78.7<br>83.6 | 100<br>98.3 | 100<br>96.8 | 86.5<br>90.5 |

[a] Standard of reference was available for 34 of 42 patients, of whom 33 received contrast.
[b] Chest wall invasion; [c] Pulmonary embolism (PE)
[d] Two reference standards used: single sub-segmental PE (SSS-PE) considered positive CTA result (top line) or SSS-PE considered negative CTA result (bottom line); Rd = Reader
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.
CTA: computed tomography angiography

**Breast:** The major indication for dignostic breast imaging is breast cancer. Two published studies of GAD in breast imaging were found, in addition to GEMMA-1 and GEMMA-2 reviewed above(Table 30). Fifty studies with MAG met the review criteria and the five largest studies are shown in Table 31. Four DOT studies met the review criteria (Table 32).

**Table 30: Literature Review Gadovist Diagnostic efficacy in breast imaging**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Malignant Lesions | Benign Lesions | | | | |
| Schmitz et al., 2008 [99] | 56[a] | 25 | 31 | 100 | 74 | 76 | 100 |
| Pediconi et al., 2013 [87] | 102[b] | 95 | 7 | 82.3[c]<br>92.6[d] | –<br>– | –<br>– | –<br>– |

[a] A total of 56 lesions were evaluated in 54 patients
[b] A total of 102 lesions were evaluated in 72 patients
[c] Lesion detection, [d] Lesion characterisation
PPV: Positive predictive value, NPV: Negative predictive value

**Table 31: Literature Review Magnevist Diagnostic efficacy in characterisation of breast lesions (top and middle) and Special studies in breast imaging: diagnostic value of specific imaging findings**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Malignant Lesions | Benign Lesions | | | | |
| Razek et al 2012 [92] | 240 patients | 88 | 152 | 93.6 | 77.9 | *67.2* | 96.2 |

PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Malignant Lesions | Benign Lesions | | | | |
| Leach et al. 2005 [67] | 649 | 35 | 614 | 77 | 81 | *19* | *98* |

PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Malignant Lesions | Benign Lesions | | | | |
| Fischer et al. 2004 [34] | 793 | 514 | 279 | 63[a] | 85.3[a] | 88.8[a] | 55.6[a] |
| Dietzel et al. 2010 [25] | 1084 | 648 | 436 | 47[b] | 88[b] | 85[b] | *53*[b] |
| Baltzer et al 2010 [7] | 316[c] | 199 | 117 | 15.4 | 99 | *90* | *66.5* |

[a] Based only on the presence of blooming sign
[b] Based only on the presence of the adjacent vessel sign
[c] Results are for diagnostic efficacy of ductal obstruction. 296 lesions showed negative ductal obstruction and 20 showed positive ductal obstruction.
PPV: Positive predictive value, NPV: Negative predictive value, Number in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.

**Table 32: Literature Review Dotarem Diagnostic efficacy in imaging of the breast**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Malignant Lesions | Benign Lesions | | | | |
| Caproni et al. 2010 [14] | 43[a] | 32 | 11 | 100 | 64 | 89 | 100 |
| Pinker et al. 2009 [88] | 55[b] | 37 | 18 | 100 | 72.2 | *88* | 100 |
| Fornasa et al., 2011 [36] | 78 | 35 | 43 | 94.3 | 93 | 91.7 | 95.2 |
| Pinker-Domenig et al. 2012 [89] | 241[c] | 169 | 72 | 99 | 81 | 92 | 97 |

[a] A total of 43 lesions were detected in 39 patients.
[b] A total of 55 lesions were detected in 34 patients.
[c] A total of 241 lesions were detected in 150 patients.
PPV: Positive predictive value, NPV: Negative predictive value, Number in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article

The sensitivity and specificity of MAG were compared with unenhanced imaging for unifocal and multifocal cancers and benign lesions. Overall, sensitivity and specificity rates for GAD, MAG and DOT supported the value of CE-MRI compared with unenhanced MRI. Sensitivity rates ranged from 82.3%-100% for GAD (Schmitz, 2008; Pediconi, 2013), 77%-93.6% for MAG (Razek, 2012; Leach, 2005), and 94.3%-100% for DOT (Caproni, 2010; Pinker, 2009; Fornasa, 2011; Domenig, 2012), Sensitivity rates for MAG used for special studies including ductal carcinoma were both lower and inconsistent (Fischer, 2004; Dietzel, 2010; Baltzer, 2010). Specificity rates ranged from 74% for GAD, 77.9%-99% for MAG, and 64%-93% for DOT. CE-MRI has the highest sensitivity rates compared with other imaging modalities and it is able to detect otherwise occult contralateral malignancies in 3% to 4% of breast cancer patients

(Lehman, 2007). PET and PET/CT imaging techniques are being reserched but are yet to show increased sensitivity compared with CE-MRI. Breast cancer imaging guidelines have been developed in both Europe and the USA and all emphasise the importance of breast CE-MRI and XRM. Guidelines published by the European Society of Breast Imaging (www.eusobi.org), the American College of Radiology www.acr.org), the European Society of Breast Cancer Specialists (Sardanelli, 2010), and the American Society of Breast Surgeons (www.breast surgeons.org) all recommend a combination of XRM and gadolinium-containing CE-MRI for screening, diagnosis and treatment monitoring in multiple clinical settings. These include screening of high risk patients, determining ipsilateral tumour extent or the presence of contralateral disease and monitoring response to neoadjuvant chemotherapy.

*6.1.2.2.2. Abdomen*

**Pancreas, gallbladder and spleen:** Only two studies of GAD in the detection of pancreatic cancer were found and neither met the review criteria. Three of four MAG studies of met the review criteria for pancreatic cancer and one for chronic pancreatitis (Tables 33-35).

**Table 33: Literature Review Magnevist Diagnostic efficacy in tumour characterisation in the pancreas**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Richter et al. 2001 [94] | 134 | 113[a] | 21 | 99.1 | 95.2 | 99.1 | 95.2 |
| Thoeni et al. 2000 [114] | 28 | 20[b] | 8 | 60 | *100* | 100 | *50* |

[a] Tumor characterization (malignant versus benign) in 134 of 143 patients. In 9 patients, no tumor was seen on MRI; these patients were not included in the evaluation of sensitivity and specificity.
[b] Insulinoma ≤ 2cm in diameter (patients with larger tumors were excluded)
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.

**Table 34: Literature Review Diagnostic efficacy in staging of pancreatic tumours**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Sironi et al. 1995 [105] | 53 | 26[a] | 27 | 81 | 100 | 100 | 87 |
| Lentschig et al. 1996 [68] | 28 | 18[b] | 10 | 94 | 70 | *85* | *87* |

[a] Tumor encasement in patients with biopsy-proven pancreatic carcinoma
[b] Nonresectable tumor found at laparoscopy
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.

**Table 35: Literature Review Magnevist Diagnostic efficacy in the diagnosis of chronic pancreatitis**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Balci et al. 2006 [5] | 30 | 11 | 19 | 82 | 57 | 56 | 86 |

PPV: Positive predictive value, NPV: Negative predictive value

Sensitivity rates ranged from 60%-99.1% and specificity rates ranged from 57%-100% (Richter, 2001; Thoeni, 2000; Sironi, 1995; Lentschig, 1996; Balci, 2006). One DOT study of pancreatic tumours was discovered with sensitivity and specificity rates of 65% and 83%, respectively (Bali, 2011). One MAG study showed diagnostic efficacy in the detection of gallbladder carcinoma (Yoshimitsu, 2012) (Table 36). No studies of the spleen met the search criteria. CT remains the diagnostic investigation of choice but CE-MRI has value when additional investigations are required (Kinney, 2010).

**Table 36: Literature Review Magnevist Diagnostic efficacy in the diagnosis of T2 gallbladder carcinoma**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | T2 lesions[a] | T1 lesions[b] | | | | |
| Yoshimitsu et al 2012 [131] | 32[c] | 21 | 11 | 86 | 91 | 95 | 77 |

[a]T2 lesions (confined to subserosal or perimuscular connective tissue)
[b]T1 lesions (confined to a muscular layer)
[c]32 lesions in 30 patients
PPV: Positive predictive value, NPV: Negative predictive value

*6.1.2.2.3. Other abdominal indications (colon, small intestine):*

No GAD studies met the inclusion criteria for bowel disorders. Twelve MAG studies (with the largest five studies included in the review) and two DOT studies met the inclusion criteria, mainly for Crohn's disease and abdominal malignancy (Table 37). Overall, sensitivity and specificity were high with the use of both MAG and DOT. Sensitivity rates ranged from 32%-98% for MAG (Kerker, 2008; Vliegen, 2005; Heverhagen, 2008; Girometti, 2008; Wallihan, 2012), and from 11%-84% for DOT (Zappa, 2011; Soussan, 2012). Specificity rates ranged from 40%-100% and 63.6%-82% for Mag and DOT, respectively. MRI can identify nearly all GI abnormalities and has value in a range of clinical settings (Ajaj, 2005; Horsthuis, 2005).

**Table 37A: Literature Review Magnevist Diagnostic efficacy in colonography/MR of rectal cancer (top) in the diagnosis of the involvement of the terminal ileum in Chrohn's disease (bottom)**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Kerker et al. 2008 [56] | 103 | 44[a] | - | 32 | NA | NA | NA |
| Vliegen et al. 2005 [124] | 83 | 63[b] | 20 | 87/98 | 60/40 | 87/84 | 60/89 |
| Heverhagen et al. 2008 [45] | 55 | 47[c] | 8 | 96/94 | 88/88 | *98/98* | *78/70* |

[a]Polyps of any size
[b]Tumor penetration of the rectal wall. Results presented by reader.
[c]Acute colonic diverticulitis. Results presented by reader.
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Girometti et al. 2008 [41] | 45[a] | 14/15[a] | 16 | 93.1 | 87.5 | 93.1 | 87.5 |

[a]45 of 52 patients included in the evaluation. Disease activity was categorized as mild, moderate to severe, and no activity/quiescent (i.e., without disease). Understaging and overstaging were defined as false negative and false positive, respectively.
PPV: Positive predictive value, NPV: Negative predictive value

**Table 37B: Literature Review Magnevist Diagnostic efficacy in inflammatory bowel disease (top); Dotarem Diagnostic efficacy in inflammation in the small bowel in Crohn's disease (middle) and in assessing peritoneal carcinomatosis from gastrointestinal malignancy (bottom)**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Wallihan et al., 2012 [125] | 45[a] | Unclear | Unclear | 92/92[b] | 100/75[b] | 100/94[b] | 73/67[b] |

[a] Comparison histopathology available in 45 out of 91 patients
[b] Results presented by reader
PPV: Positive predictive value, NPV: Negative predictive value

| Study | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients with inactive disease | | | | |
| Zappa et al. 2011 [132] | 53 | 51 | 2 | 63.6[a] | 92.9[a] | *94.1*[a] | *31.4*[a] |

[a] Wall thickness threshold of 6 mm
PPV: Positive predictive value, NPV: Negative predictive value.
Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article

| Study | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Soussan et al. 2012 [107] | 30 | 19 | 11 | 84 | 82 | 89 | 75 |

[a] In this study, MR with diffusion-weighted imaging (DWI) was used
PPV: Positive predictive value, NPV: Negative predictive value

### *6.1.2.3. Pelvis*

#### *6.1.2.3.1. Male (prostate and bladder):*

Two GAD studies met the inclusion criteria for prostate cancer. In one of these studies, a prospective study in 150 patients (Panebianco, 2010), sensitivity, specificity and accuracy were 76.5%, 89.5% and 88.2%, respectively. A total of 22 MAG studies of the male pelvis met the inclusion criteria and the largest five studies were reviewed (Table 38).

**Table 38: Literature Review Magnevist Diagnostic efficacy of contrast-enhanced MRI tumour detection in prostate cancer (top), in characterisation in the prostate (middle) and tumour staging in prostate cancer (bottom)**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Tanimoto et al. 2007 [110] | 83 | 44[a] | 39 | 95 | 74 | *80* | *93* |
| Cirillo et al. 2009 [21] | 72 | 44[b] | 28 | 84.1 | 89.3 | 92.5 | 78.1 |
| Turkbey et al. 2010 [119] | 70 | 70[a] | 0 | *80* | NR | NR | NR |

[a] Prostate cancer
[b] Recurrence of prostate cancer following radical prostatectomy
PPV: Positive predictive value, NPV: Negative predictive value, NR: Not relevant, Numbers in *italics* were calculated from information provided in the article.

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Li et al. 2006 [69] | 86[a] | 53 | 33 | 66 | 75 | 81 | 58 |

[a] Transition zone lesions (malignant vs. benign). Total population studied: 116.
PPV: Positive predictive value, NPV: Negative predictive value

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Fuetterer et al. 2005 [37] | 99 | 35[a] | 64[a] | 69 | 97 | 92 | 85 |

[a] Tumor stage 3 versus tumor stage 2. All patients had biopsy-proven prostate cancer.
PPV: Positive predictive value, NPV: Negative predictive value

The results were inconsistent with significantly increased sensitivity and specificity for CMRM in only two studies (Tanimoto, 2007; Cirillo, 2009). Similar results were obtained in the five DOT studies that met the inclusion criteria, all involving the prostate (Table 39).

**Table 39: Literature Review Dotarem Diagnostic efficacy of different MR techniques for the diagnosis of prostate cancer or detection of localised prostate cancer (top) and positive predictive value of MRI value in patients with suspicion of recurrent prostate cancer**

| Study Module 5.4 | Sample Size | | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|---|
| | Total | Method | Patients with disease | Patients without disease | | | | |
| Portalez et al. 2004 [90] | 32 | T2-weighted | 15 | 17 | 47 | NR | NR | NR |
| | | DCE | 15 | 17 | 53 | NR | NR | NR |
| | | Spectroscopy | 15 | 17 | 67 | NR | NR | NR |
| Ben Cheikh et al. 2009 [10] | 83 | T2-weighted | 23 | 60 | 47.8 | 44.3 | 20.4 | 79.5 |
| | | DCE | 23 | 60 | 82.6 | 20 | 24.4 | 93.3 |
| Hoeks et al., 2013 [46] | 63 | T2-weighted + DCE | 28 | 35 | 53 | 76 | NR | NR |
| Jambor et al., 2012 [49] | 33[a] | Anatomical + DCE-MRi | 50 lobes | 22 lobes | 85[b] | 37[b] | NR | NR |

[a] 33 of 36 patients underwent MRI
PPV: Positive predictive value, NPV: Negative predictive value, NR: Not reported, DCE: Dynamic contrast enhancement

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Rouviere et al. 2010 [95] | 54 | 40 | 14 | NA | NA | 53[a] | NA |

[a] Based on 41 malignant lesions at biopsy and 77 suspicious MR findings
PPV: Positive predictive value, NPV: Negative predictive value, NA: Not applicable, Number in *italics* was determined from information provided in the report.

Sensitivity ranged from 47%-85% and specificity ranged from 20%-76%. The introduction of endorectal-coil imaging with MR spectroscopy, dynamic CE-MRI and diffusion-weighted

imaging has significantly increased the accuarcy of MRI in recent years. No publications were found for GAD and the bladder and the single DOT study did not meet the inclusion criteria. Five MAG studies were identified and four met the inclusion criteria (Table 40).

**Table 40: Literature Review Magnevist in Diagnostic efficacy in staging of bladder cancer (top) and patients with urinary obstruction (bottom).**

| Study Module 5.4 | Sample Size: Total | Patients with disease or number of lesions[a] | Patients without disease or with besign lesions | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| Tekes et al. 2005 [112] | 71 | 38 | 33 | 97/95 | 67/55 | 77/71 | 96/90 |
| Takeuchi et al. 2009 [109] | 52[b] | 17[b] | 35[b] | 94 | 86 | *77* | *97* |
| Watanabe et al. 2009 [126] | 19 | 5a | 14 | 80 | 79 | *58* | *92* |

[a] Accuracy of MRI in differentiating invasive (≥ T2) tumors from superficial (≤ T1) tumors
[b] 52 tumors from 40 patients were evaluated
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.

| Study Module 5.4 | Sample Size: Total | Patients with disease[a] | Patients with other obstructive disease | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| Erdogmus et al. 2004 [30] | 29 | 22 | 7 | *82*[b] | 89 | *95* | *67* |

[a] Urinary stones (a total of 31 obstructions were confirmed in 29 patients)
[b] Recalculated. The original report states 18 of 22 stones were correctly identified by contrast-enhanced MRI but reports the sensitivity as 77%. In the original report, the column labels for sensitivity and specificity are also inverted (sensitivity labeled as specificity and vice versa).
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.

Only small patient numbers of bladder cancer and urinary obstruction were studied with inconsistent results (Tekes, 2005; Takeuchi, 2009; Watanabe, 2009; Erdogmus, 2004). Sensitivity and specificity rates ranged from 80%-97% and 55%-89%, respectively.

*6.1.2.3.2. Female (uterus and cervix):*

Four GAD articles studying imaging of the uterus were identified, one of which met the inclusion criteria (Table 41).

**Table 41: Literature Review Gadovist Diagnostic efficacy in imaging of the uterus: prediction of success of uterine artery embolisation**

| Study Module 5.4 | Sample Size: Total | Successful | Not successful | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| Sipola et al. 2010 [104] | 47[a] | 13 | 34 | 85 | 62 | 46 | 91 |

[a] 47 of 52 patients were included in the analyses
PPV: Positive predictive value, NPV: Negative predictive value

In a study of tumour imaging in 47 patients, sensitivity and specificity were 85% and 62%, respectively (Sipola, 2010). Nine MAG studies met the inclusion criteria and the five largest were reviewed (Table 42).

**Table 42: Literature Review Diagnostic efficacy in staging of tumours in the female pelvis (top), for prediction of outcomes in tumours of the female pelvis (middle) and in lesion characterisation of adnexal masses (bottom).**

| Study Module 5.4 | Sample Size: Total | Patients with disease | Patients without disease | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| Choi et al. 2004 [19] | 115 | 23[a] | 91 | 87 | 79 | 51 | 96 |
| | | 17[b] | 96 | 36 | 97 | 57 | 93 |
| Lin et al. 2009 [70] | 48 | 33[c] | 15 | 85 | 60 | 82 | 54 |
| | | 7[d] | 41 | 100 | 93 | 70 | 100 |
| Gao et al., 2012 [38] | 36 | 10[e] | 26 | 50 | 84.6 | 55.6 | 81.5 |
| | | 26[f] | 10 | 80 | 100 | 100 | 92.9 |
| | | 6[g] | 30 | 50 | 100 | 100 | 90.9 |
| | | 30[h] | 6 | 66.7 | 100 | 100 | 93.8 |

[a] Patients with vaginal invasion of cervical cancer
[b] Lymph node involvement
[c] Myometrial involvement
[d] Deep myometrial involvement
[e] Stage Ic Group 1 (unenhanced); [f] Stage Ic Group 2 (unenhanced + enhanced); [g] Stage II Group 1 (unenhanced); [h] Stage II Group 2 (unenhanced + enhanced)
PPV: Positive predictive value, NPV: Negative predictive value

| Study Module 5.4 | Sample Size: Total | Patients with poor outcome | Patients with good outcome | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| Low et al. 2005 [72] | 76 | 68[a] | 8 | 90 | 88 | 98 | 50 |

[a] Residual tumor
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.

**Table 2-31: Magnevist® - Diagnostic efficacy in lesion characterization of adnexal masses**

| Study Module 5.4 | Sample Size: Total | Patients with disease | Patients without disease | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| Kawahara et al 2004 [54] | 49 | 23[a] | 26 | 91 | 87 | *86* | *92* |

[a] Ovarian cancer
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.

The study results were inconsistent but overall CMRI was shown to have value, particularly in assessment of the endometrium (Choi, 2004; Lin, 2009; Gao,2012; Low, 2005; Kawahara, 2004). Sensitivity and specificity rates ranged from 23.1%-100% and 83.3%-100%, respectively. Similar findings were observed in the five DOT studies reviewed (Bazot, 2004; Chamie, 2009; Bazot, 2011; Torricelli, 2008; Thomassin-Naggara, 2008). Sensitivity and specificity rates ranged from 62.5%-100% and 81%-100%, resectively. CE-MRI was shown to have high sensitivity and specificity in endometriosis, endometrial carcinoma and ovarian tumours.

*6.1.2.3.3. Extremities and musculoskeletal system:*

Five studies of GAD for the imaging of extremities and the musculoskeletal system were discovered but none met the inclusion criteria. Sixteen MAG studies met the inclusion criteria and the largest five were reviewed (van Rijswijk, 2004; Tokuda, 2009; Averill, 2009; Calder, 2008; Sen, 2010) Table 43).

**Table 43: Literature Review Magnevist Diagnostic efficacy in musculoskeletal imaging**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| van Rijswijk et al. 2004 [122] | 111 | 54[a] | 57 | 70/82[b] | 81/83[b] | *78/82*[b] | *74/83*[b] |
| Tokuda et al. 2009 [117] | 67 | 33[a] | 34 | 97/84.8[b] | 58.8/47.1[b] | *70/61*[b] | *95/76*[b] |
| Averill et al 2009 [4] | 78 | 40[c] | 38 | 83 | 79 | *81* | *82* |
| Calder et al. 2008 [13] | 60 | 40[d] | 20 | 51 | 90 | 48 | 86 |
| Sen et al. 2010 [103] | 55 | 23[a] | 32 | 83 | 81 | 76 | 87 |

[a] Malignant vs. benign
[b] Results presented by reader
[c] Osteomyelitis
[d] Osteonecrosis in the proximal femur. 4 anatomic regions were evaluated in each of 15 patients.
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics* were calculated from information provided in the article

Most investigations related to soft tissue tumours. Overall sensitivity and specificity rates for MAG were high but not significantly superior to unenhanced imaging. Two DOT studies were reviewed, one for indirect arthrography for supraspinatus tears (van Dyck, 2009). This study demonstrated no value for CMRI. However, CMRI was shown to be useful in children with osteoarticular infections (Kanavaki, 2012).

**Whole body:** No studies of GAD or DOT for whole body imaging were discovered. One large MAG study evaluated the use of MAG in the assessment of patients with stage 3 or 4 melanoma (Hausmann, 2011) (Table 44). Sensitivity and specificity were 73.4% and 83.7%, respectively. MRI was slightly less sensitive than CT but specificity was significantly higher for MRI.

**Table 44: Literature Review Magnevist Diagnostic efficacy using whole body MRI for melanoma**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Number of malignant lesions | Number of benign lesions | | | | |
| Hausmann et al., 2011 [43] | 824 lesions in 33 patients | 455 | 369 | 73.4 | 83.7 | *84.8* | *71.8* |

PPV: Positive predictive value, NPV: Negative predictive value
Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article

**Comment:** The literature review to support the whole body indication had two main objectives. The first objective was to assess the sensitivity, specificity and diagnostic accuracy in the comparison of CE-MRI versus UMRI. The second objective was to assess the non-inferiority of Gadovist compared with two leading comparator contrast agents. Publications relating to Gadovist® (n=21), Magnevist (n=58) and Dotarem (35) for the imaging of different body areas are summarised with particular emphasis on breast cancers. There is an extensive literature relating to Gadovist and other marketed gadolinium-containing contrast agents. The literature review submitted by the sponsor to support whole body imaging complies with search criteria agreed with the TGA to minimise reporting bias. Publications which met the search criteria employed a range of methodologies and study designs with emphasis on specific pathologies and target organs. The publications were of inconsistent value with considerable variability in patient numbers, power and statistical validity. Some studies were retrospective, some were uncontrolled, and some were not randomised. Nonetheless, the great weight of literature evidence confirms the clinical value of CE-MRI compared with UMRM, and the non-inferiority of GAD compared with two widely used gadolinium containing comparators.

## 6.2. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

## 6.3. Evaluator's conclusions on clinical efficacy for Indication 1:

Contrast enhancement in whole body MRI including head and neck region, thoracic space, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus), retroperitoneal space (kidney), extremities and musculoskeletal system.

The most relevant pivotal study to support the proposed whole body indication is 13297, a Phase III, blinded comparison of GAD versus MAG for whole body imaging. The study was well designed and conducted with care taken to ensure blinded reporting of the MRI images. The results of the study clearly demonstrate the superiority of GAD compared with unenhanced MRI, and the non-inferiority of GAD compared with MAG for all primary and secondary endpoints used to assess sensitivity, specificity and diagnostic accuracy. The study was not powered to confirm non-inferiority for all body regions but the results for individual organs were compatible with the overall results. Although, the study was conducted in an Asian population, the results are applicable to other racial groups. Study 94055/99012 was a post hoc analysis of an open-label study with blinded readers which supported the conclusions of 13297. GAD proved superior to unenhanced MRI in 151 evaluable patients for the visualisation of various body regions and organs. The results of GEMMA-1 and GEMMA-2 confirmed the superiority of GAD versus unenhanced imaging for breast cancer, and the value of GAD when used with other imaging techniques such as XRM.

The literature search supported the use of GAD for whole body imaging. Published data support the value of GAD compared with unenhanced imaging and the results were comparable with two leading contrast agents in the same class. The literature relating to Gadovist® is less extensive compared with the comparators. However, for almost all body areas, there are sufficient data to confirm the value of CE-MRI compared with UMRI for the three contrast agents reviewed. Superior sensitivity, specificity and diagnostic accuracy have been demonstrated, in particular for the diagnosis and follow-up of cancers. In addition, similar rates for sensitivity, specificity and diagnostic accuracy have been reported for all three contrast agents. Overall, the literature review of efficacy supports the conclusions of study 13297 which clearly confirmed the non-inferiority of Gadovist® compared with Magnevist® for whole body imaging.

## 6.4. Indication 2

**Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement**

### 6.4.1. Study 305501

This was a multicentre, double-blind, randomised dose finding study of GAD in myocardial perfusion MRI. It was conducted in 14 centres in Germany, Austria, Poland and Switzerland. The first enrolment was in March 2004 and the study completed in 2006. The primary objective was to evaluate the diagnostic efficacy of four increasing doses of GAD in the detection of myocardial perfusion defects. Eligible patients were male or female with reversible focal hypoperfusion in at least two adjoining segments on SPECT performed within 4 weeks of study enrolment. First pass contrast-enhanced CMRI during stress and at rest were compared with SPECT imaging during stress and at rest. Two injections of Gadovist® 1.0 at doses of 0.01, 0.025, 0.05, or 0.1 mmol/kg BW were administered to each patient according to the randomisation list. A total of 240 patients were planned with at least 40 evaluable patients in each group. A total of 232 patients were enrolled and there were 226, 222 and 207 patients in the SAF, FAS and PPS, respectively (Table 45).

**Table 45: Study 305501 Number and % of patients assigned to different analysis sets by treatment (randomised patients).**

| | All patients | SH L 562 BB 0.01 mmol/kg | SH L 562 BB 0.025 mmol/kg | SH L 562 BB 0.05 mmol/kg | SH L 562 BB 0.1 mmol/kg |
|---|---|---|---|---|---|
| Number of patients | 232 (100.0%) | 58 (100.0%) | 60 (100.0%) | 59 (100.0%) | 55 (100.0%) |
| Listing only set | | | | | |
| no | 226 ( 97.4%) | 54 ( 93.1%) | 60 (100.0%) | 58 ( 98.3%) | 54 ( 98.2%) |
| yes | 6 ( 2.6%) | 4 ( 6.9%) | 0 | 1 ( 1.7%) | 1 ( 1.8%) |
| Safety analysis set | | | | | |
| no | 6 ( 2.6%) | 4 ( 6.9%) | 0 | 1 ( 1.7%) | 1 ( 1.8%) |
| yes | 226 ( 97.4%) | 54 ( 93.1%) | 60 (100.0%) | 58 ( 98.3%) | 54 ( 98.2%) |
| Full analysis set | | | | | |
| no | 10 ( 4.3%) | 6 ( 10.3%) | 0 | 3 ( 5.1%) | 1 ( 1.8%) |
| yes | 222 (95.7%) | 52 ( 89.7%) | 60 (100.0%) | 56 ( 94.9%) | 54 ( 98.2%) |
| Per protocol set | | | | | |
| no | 25 ( 10.8%) | 14 ( 24.1%) | 3 ( 5.0%) | 6 ( 10.2%) | 2 ( 3.6%) |
| yes | 207 ( 89.2%) | 44 ( 75.9%) | 57 ( 95.0%) | 53 ( 89.8%) | 53 ( 96.4%) |

The primary efficacy endpoint was the agreement rate between GAD-enhanced MRI and SPECT diagnoses based on the correct visual assessment of three coronary territories in a blinded read. Central evaluation of the images was performed by three blinded readers, with the average rate used to assess overall efficacy. Baseline demographic data were comparable in the four treatment groups. All but one patient were White. Most were male (range 64.8% to 72.2%) with mean age ranging from 59.7 to 62.9 years and mean body weight ranging from 78.75 to 82.02 kg. The characteristics of the coronary heart disease at baseline are shown in Table 46. Most patients had a history of coronary artery disease.

**Table 46: Study 305501 Characteristics of the coronary heart disease at baseline by treatment (SAF)**

| | SH L 562 BB 0.01 mmol/kg N (%) | SH L 562 BB 0.025 mmol/kg N (%) | SH L 562 BB 0.05 mmol/kg N (%) | SH L 562 BB 0.1 mmol/kg N (%) |
|---|---|---|---|---|
| Number of patients | 54 (100.0%) | 60 (100.0%) | 58 (100.0%) | 54 (100.0%) |
| History of coronary artery disease | | | | |
| no | 19 ( 35.2%) | 27 ( 45.0%) | 21 ( 36.2%) | 20 ( 37.0%) |
| yes | 35 ( 64.8%) | 33 ( 55.0%) | 37 ( 63.8%) | 34 ( 63.0%) |
| If yes,[a] | | | | |
| - presence of history of PTCA | 21 ( 60.0%) | 16 ( 48.5%) | 19 ( 51.4%) | 15 (44.1%) |
| - previous history of stent placement | 17 ( 48.6%) | 14 ( 42.4%) | 16 ( 43.2%) | 13 (38.2%) |
| - presence of history of coronary bypass | 5 ( 14.3%) | 9 ( 27.3%) | 7 ( 18.9%) | 6 (17.6%) |
| History of myocardial infarction | | | | |
| no | 34 ( 63.0%) | 42 ( 70.0%) | 43 ( 74.1%) | 37 ( 68.5%) |
| yes | 20 ( 37.0%) | 17 ( 28.3%) | 15 ( 25.9%) | 15 ( 27.8%) |
| unknown | 0 | 1 ( 1.7%) | 0 | 2 ( 3.7%) |
| CCS classification of angina severity | | | | |
| I | 19 ( 35.2%) | 24 ( 40.0%) | 20 ( 34.5%) | 20 ( 37.0%) |
| II | 28 ( 51.9%) | 32 ( 53.3%) | 31 ( 53.4%) | 27 ( 50.0%) |
| III | 7 ( 13.0%) | 3 ( 5.0%) | 6 ( 10.3%) | 6 ( 11.1%) |
| IV | 0 | 1 ( 1.7%) | 0 | 0 |
| not applicable | 0 | 0 | 1 ( 1.7%) | 0 |
| not assessable | 0 | 0 | 0 | 1 ( 1.9%) |
| NYHA classification of angina severity | | | | |
| I | 27 ( 50.0%) | 34 ( 56.7%) | 25 ( 43.1%) | 26 ( 48.1%) |
| II | 20 ( 37.0%) | 24 ( 40.0%) | 28 ( 48.3%) | 26 ( 48.1%) |
| III | 7 ( 13.0%) | 1 ( 1.7%) | 5 ( 8.6%) | 2 ( 3.7%) |
| IV | 0 | 1 ( 1.7%) | 0 | 0 |

[a] % calculated taking the number of patients with coronary artery disease as 100%

#### *6.4.1.1. Efficacy results*

The agreement rates between GAD-enhanced MRI and SPECT are shown in Table 47. In the PPS, region-based agreement rates ranged from 41.2% in the lowest dose group to 59.7% in the highest dose group.

**Table 47: Study 305501 Agreement rate between Gadovist 1.0 perfusion MRI diagnosis (blinded reading) and SPECT diagnosis (central reading) in the detection of cardiac perfusion deficits based on regions and based on segments by treatment for the average reader (PPS)**

| | SH L 562 BB 0.01 mmol/kg N (%) | SH L 562 BB 0.025 mmol/kg N (%) | SH L 562 BB 0.05 mmol/kg N (%) | SH L 562 BB 0.1 mmol/kg N (%) |
|---|---|---|---|---|
| Number of patients | 44 (100.0%) | 57 (100.0%) | 53 (100.0%) | 53 (100.0%) |
| **Average reader by region** | | | | |
| Number of assessments | 396 (100.0%) | 513 (100.0%) | 477 (100.0%) | 477 (100.0%) |
| Disagreement | 233 ( 58.8%) | 226 ( 44.1%) | 175 ( 36.7%) | 192 ( 40.3%) |
| Agreement | 163 ( 41.2%) | 287 ( 55.9%) | 302 ( 63.3%) | 285 ( 59.7%) |
| **Average reader by segment** | | | | |
| Number of assessments | 2112 (100.0%) | 2736 (100.0%) | 2544 (100.0%) | 2544 (100.0%) |
| Disagreement | 1079 ( 51.1%) | 1079 ( 39.4%) | 878 ( 34.5%) | 868 ( 34.1%) |
| Agreement | 1033 ( 48.9%) | 1657 ( 60.6%) | 1666 ( 65.5%) | 1676 ( 65.9%) |

Note: Number of assessments is the number of patients multiplied with the number of assessed segments (n=16) and regions( n=3), respectively, and, in case of the average blinded reader, multiplied with the total number of blinded readers (n=3). For definition of the "average reader" refer to Section 11.4.1.

Agreement rates were comparable in the FAS. The confidence intervals for each assessment were shown. There was a statistically significant difference between the three highest and the lowest dose group indicating that the lowest dose of GAD was ineffective for cardiac perfusion MR. The agreement rates in the 0.025 mmol/kg BW group were higher than in the lowest dose group. The agreement rates in the 0.05 mmol/kg BW dose group were 65.5% (based on segments) and 63.3% (based on regions) compared with 65.9% and 59.7%, respectively, in the 0.1 mmol/kg BW dose group. There was no benefit in favour of the highest dose and the 0.05 mmol/kg BW was considered the most appropriate dose for further myocardial perfusion clinical trials.

### 6.4.2. Literature review

**Heart:** Cardiac imaging is the most intensively researched indication for CMRI, typically divided into cardiac perfusion imaging, delayed enhancement and cardiac anatomy. However, no publications relating to cardiac anatomy met the inclusion criteria for GAD, MAG or DOT. Thirteen GAD publications met the inclusion criteria, most commonly related to delayed enhancement (DE) and DE perfusion studies. Cardiac studies comprised 30% of all MAG studies and 62 publications met the review criteria. Eight DOT studies met the review criteria.

**Cardiac perfusion imaging:** A total of eight studies investigated the sensitivity and specificity of GAD, seven of which used a stress/rest protocol (imaging with vasodilator stress with later imaging when the effects of the vasodilator had subsided). One study used a rest/stress protocol in which the imaging sequence was reversed. In seven of the studies, a DE imaging sequence was performed after the perfusion studies to determine the presence of myocardial infarction. Doses ranged from 0.025 to 0.1 mmol/kg with separate doses administered for the rest and stress perfusion studies. GAD provided good image quality and high accuracy for detection of significant coronary artery disease. Across all GAD studies, sensitivity ranged from 82.8% to 98%, and specificity ranged from 79% to 100% (Meyer, 2008; Thomas, 2008; Fenchel, 2007; Kuehl, 2007; Scheffel, 2010; Klumpp, 2010; Donati, 2010; Jogiya, 2012) (Table 48). In a pooled analysis of all studies, sensitivity and specificity were 91% and 89%, respectively.

**Table 48: Literature Review Gadovist Diagnostic efficacy in myocardial perfusion imaging**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Patients with disease | Patients without disease | | | | |
| Meyer et al. 2008 [178] | 60 | 36 | 24 | 89 | 79 | 83 | 85 |
| Thomas et al. 2008 [261] | 60 | 28[a] | 32[a] | 93 | 84 | --[a] | --[a] |
| Fenchel et al. 2007 [77] | 25 | 18 | 7 | 89 | 94 | *94* | *75* |
| Kuehl et al. 2007 [143] | 28 | 19 | 9 | 94 | 100 | *100* | *94* |
| Scheffel et al. 2010 [234] | 43 | 29 | 14 | 82.8 | 100 | 100 | 73.7 |
| Klumpp et al. 2010 [135] | 57 | 41 | 16 | *95/98*[b] | *88/92*[b] | *93/95*[b] | *92/96*[b] |
| Donati et al. 2010 [68] | 47 | 33 | 14 | 90.9 | 100 | 100 | 82.4 |
| Jogiya et al., 2012 [121] | 53 | 34 | 19 | 91.2 | 89.5 | 93.9 | 85.0 |
| ***Overall*** | ***373*** | ***238*** | ***135*** | ***91*** | ***89*** | ***93*** | ***86*** |

[a] Calculated from the authors' assertion that the prevalence of disease was 47%. Internal evidence in the article suggest that the prevalence may have been significantly higher, because 45 of 60 patients are described as having coronary artery disease. PPV and NPV were therefore not calculated.
[b] Results were presented separately for each of 2 independent readers.
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article.
Overall: weighted average of all studies. For Klumpp et al, only data from Reader 1 was utilized.

The five largest cardiac perfusion studies using MAG for the diagnosis of coronary artery disease were reviewed and in each case perfusion imaging was followed by DE imaging. Across all studies, sensitivity ranged from 73% to 93% and specificity ranged from 77% to 90% (Bernhardt, 2009; Merkle, 2007; Merkle, 2010; Doesch, 2008; Gebker, 2012). Two studies of DOT for perfusion imaging met the inclusion criteria. Sensitivity ranged from 92% to 96% and specificity ranged from 82% to 87% (Bernhardt, 2006; Falcao, 2013). The diagnostic accuracy of GAD was broadly similar to that of both MAG and DOT.

**Delayed enhancement:** Five GAD imaging studies of delayed enhancement alone (not associated with perfusion imaging) met the inclusion criteria, one of which included GAD as the test CE (Seeger, 2012). The study results demonstrated clear value for GAD for the location and extent of myocardial infarction.

A total of 29 studies of delayed enhancement with MAG met the inclusion criteria and the five largest studies were reviewed (Table 49).

**Table 49: Literature Review Magnevist Diagostic efficacy of delayed enhancement in various clinical settings**

| Stu Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | | Patients with disease | Patients without disease | | | | |
| Diagnostic Question: Etiology of left ventricular dysfunction | | | | | | | |
| Valle-Munoz et al. 2009 [270] | 100 | 21[a] | 79 | 85.7 | 92.4 | *75* | 96 |
| Casolo et al. 2006 [46] | 60 | 41[a] | 19 | 98 | 84 | *93* | *95* |
| Diagnostic Question: Localization of myocardial infarction | | | | | | | |
| Abdel-Aty et al. 2004 [1] | 54 | 54[b] | 0 | 96/98 | NA | NA | NA |
| Diagnostic Question: Diagnosis of cardiac sarcoidosis | | | | | | | |
| Smedema et al. 2005 [251] | 58 | 12[c] | 46 | 100 | 78 | 55 | 100 |

[a] Disease defined as angiographically significant coronary artery disease.
[b] Disease defined as myocardial infarction
[c] Disease defined as cardiac involvement. All 58 patients had a diagnosis of pulmonary sarcoidosis.
PPV: Positive predictive value, NPV: Negative predictive value, Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article

In the largest study of 1366 patients with known or suspected coronary artery disease, cardiac MRI using MAG was used as the reference for testing the diagnostic accuracy of ECGs (Krittayaphong, 2009 ) (Table 50).

**Table 50: Literature Review Diagnostic accuracy of electrocardiography in the detection of myocardial infarction using delayed enhancement cardiac MRI with Magnevist**

| ECG Method | Minnesota | ESC/ACC 2000 | TIMI | UD 2007 |
|---|---|---|---|---|
| True positive | 300 | 223 | 287 | 234 |
| True negative | 785 | 815 | 790 | 796 |
| False positive | 74 | 44 | 69 | 63 |
| False negative | 207 | 284 | 220 | 273 |
| Sensitivity (%) | 59 (55–63) | 44 (40–48) | 57 (52–61) | 46 (42–51) |
| Specificity (%) | 91 (89–93) | 95 (93–96) | 92 (90–94) | 93 (91–94) |

Prevalence of MI was 37.1% (n = 507), as determined by delayed enhancement.
UD 2007=ESC/ACC Foundation/American Heart Association/World Heart Foundation (universal definition) 2007.
From Table 2 in Krittayaphong et al. 2009 [142]

Two studies assessed LV dysfunction with sensitivity rates ranging from 85.7%-98%, and specificity rates ranging from 84%-92.4% (Valle-Munoz, 2009; Casolo, 2006). Localisation of myocardial infarction was assessed in one study with a sensitivity of 96% (Abdel-Aty, 2004). Six DOT studies met the inclusion criteria, five of which used DOT as the standard of reference. One study used delayed enhancement as a test procedure for predicting recovery of function in patients with dysfunctional ventricular segments after myocardial infarction (Gerbaud, 2010) (Table 51).

**Table 51: Literature Review Diagnostic efficacy of delayed enhancement in predicting recovery of function in dysfunctional ventricular segments following acute myocardial infarction**

| Study Module 5.4 | Sample Size | | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| | Total | Segments recovered function | Segments without recovery in function | | | | |
| Gerbaud et al. 2010 [93] | 314 | 165 | 149 | 64[a] | 58[a] | *63* | *59* |

[a] Absence of transmural delayed enhancement used to predict recovery of function. A total of 314 dysfunctional ventricular segments were evaluated in 69 patients.
PPV: Positive predictive value, NPV: Negative predictive value. Numbers in *italics*: Data were not provided in the original publication. Values were calculated based on information provided in the article

### 6.5. Evaluator's conclusions for Indication 2:

A single Phase 2 dose-finding study demonstrated the usefulness of GAD for cardiac perfusion and delayed enhancement at the two higher doses of 0.05 and 0.1 mmol/kg BW. The proposed indication for cardiac imaging is supported by a literature review which overwhelmingly confirms the value of cardiac imaging with CE-MRI. Cardiac MRI is now accepted as a gold standard imaging technique of particular value in the investigation of coronary artery disease. An extensive literature for MAG supports the use of cardiac MRI. A smaller number of DOT studies show similar value and the GAD literature (13 articles) is consistent with the overall findings. No studies meeting the inclusion criteria have specifically reported sensitivity and specificity for the evaluation of cardiac anatomy for GAD, MAG or DOT.

# 7. Clinical safety

### 7.1. Studies providing evaluable safety data

In the current submission, the following pivotal studies provided evaluable safety data:

- 13297
- 91743
- 91782

#### 7.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed and coded using MedDRA version 14.1 or 16.0
- AEs of interest include hypersensitivity reactions and nephrogenic systemic fibrosis
- Laboratory tests, including haematology, clinical chemistry and urinalysis were performed at central laboratories.

#### 7.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

#### 7.1.3. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study 308183 was a single dose PK study in 31 elderly and non-elderly adult patients. There were no SAEs or serious AEs and only isolated AEs were reported, mainly headache. The safety data from this study are included the Integrated Summary of Safety (ISS)
- Study 305501 provided dose-ranging data in a myocardial perfusion MRI study. Treatment-emergent AEs were reported in 5.8% of patients but there were no deaths, SAEs or severe AEs. The most frequent AEs were headache, GI disorders, and injection site reactions. The safety data from this study are included in the ISS
- Study 94055/99012 was a post hoc efficacy analysis and no additional safety analyses were presented. The safety data are included in the ISS.

#### 7.1.4. Extent of exposure

In study 13297, 178 patients received GAD (mean volume 6.28 mL) and 185 patients received MAG (mean volume 12.44 mL). In studies 91743 and 91782, all 426 and 439 patients, respectively, received the same dose of GAD 0.1 mmol/kg BW.

### 7.2. All adverse events (irrespective of relationship to study treatment)

#### 7.2.1. Pivotal studies

In study 13297: As shown in Table 52, 8% of patients reported at least one treatment-emergent AE (TEAE) (7.3% GAD, 8.6% MAG). In the GAD group, the most frequently reported AEs were feeling hot, dry mouth, pyrexia, proteinuria, headache and rash. Most AEs were considered mild.

In study 91743: As shown in Table 53, 8.2% of patients reported at least one TEAE. The most frequently reported TEAEs were nervous system disorders (2.8%), GI disorders (1.2%) and skin disorders (1.2%). Most AEs were considered mild and none were severe.

In study 91782: As shown in Table 54, 5.7% of patients reported at least one TEAE. The most frequently reported TEAEs were nervous system disorders (1.6%), GI disorders (1.4%) and general disorders and administration site conditions (1.4%). Most AEs were considered mild and none were severe.

**Table 52: Study 13297 Overall AE experience-Number (%) of subjects. Safety Analysis Set**

| | Gadobutrol (n=178) | Magnevist (n=185) | Total (n=363) |
|---|---|---|---|
| Any pre AE | 8 (4.5%) | 7 (3.8%) | 15 (4.1%) |
| Any TEAE | 13 (7.3%) | 16 (8.6%) | 29 (8.0%) |
| Drug-related TEAE | 7 (3.9%) | 3 (1.6%) | 10 (2.8%) |
| Study procedure related TEAE | 2 (1.1%) | 2 (1.1%) | 4 (1.1%) |
| Maximum intensity of TEAE | | | |
| Mild | 12 (6.7%) | 13 (7.0%) | 25 (6.9%) |
| Moderate | 1 (0.6%) | 2 (1.1%) | 3 (0.8%) |
| Severe | 0 | 1 (0.5%) | 1 (0.3%) |
| Maximum intensity of drug-related TEAE | | | |
| Mild | 7 (3.9%) | 1 (0.5%) | 8 (2.2%) |
| Moderate | 0 | 1 (0.5%) | 1 (0.3%) |
| Severe | 0 | 1 (0.5%) | 1 (0.3%) |
| Death | 0 | 0 | 0 |
| SAE | 0 | 0 | 0 |
| Discontinuation of study drug due to TEAE | 0 | 0 | 0 |

Source: Table 14.3.1/1, Table 14.3.2/15, Table 16.2.7/9
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event

**Table 53: Study 91743 Overview of AEs (SAF)**

| | Gadobutrol 0.1 mmol/ kg body weight N = 426 patients (100%) | |
|---|---|---|
| | n | (%) |
| At least 1 adverse event (AE) | 54 | ( 12.7%) |
| At least 1 treatment-emergent AE (TEAE) | 35 | ( 8.2%) |
| At least 1 drug-related TEAE | 7 | ( 1.6%) |
| At least 1 serious AE (SAE) | 0 | |
| At least 1 treatment-emergent SAE | 0 | |
| Discontinued due to AE/TEAE | 0 | |
| Discontinued due to SAE/treatment–emergent SAE | 0 | |
| Death | 0 | |
| At least 1 severe TEAE | 0 | |

**Table 54: Study 91782 Overview of AEs**

| | Gadobutrol 0.1 mmol/ kg body weight N = 439 patients (100%) | |
|---|---|---|
| | n | (%) |
| At least 1 adverse event (AE) | 45 | ( 10.3%) |
| At least 1 treatment-emergent AE (TEAE) | 25 | ( 5.7%) |
| At least 1 drug-related TEAE | 8 | ( 1.8%) |
| At least 1 serious AE (SAE) | 0 | |
| At least 1 treatment-emergent SAE | 0 | |
| Discontinued due to AE/TEAE | 0 | |
| Discontinued due to SAE/treatment–emergent SAE | 0 | |
| Death | 0 | |
| At least 1 severe TEAE | 1 | ( 0.2%) |

### 7.2.2. Other studies

Not applicable.

## 7.3. Treatment-related adverse events (adverse drug reactions)

### 7.3.1. Pivotal studies

In study 13297: AEs considered drug related by the investigator were recorded in 3.9% of the GAD group and 1.6% of the MAG group. In the GAD group, the most frequent TEAEs were feeling hot, dry mouth, pyrexia, proteinuria, headache and rash.

In study 91743: Drug related AEs were reported by 1.6% of patients (dizziness, headache, erythema, hepatic enzyme increase, nausea, tremor and urticaria). The erythema was of moderate intensity and all the other events were mild.

In study 91782: Drug related TEAEs were reported by 8 (1.8%) of patients (nausea, eyelid oedema, diarrhoea, tongue pruritus, vomiting, facial oedema, increased bilirubin, crystalluria, erythema, pruritus, pruritic rash and urticaria).

#### 7.3.2. Other studies

The safety data from the two small non-pivotal studies were unremarkable and they are included in the Integrated Summary of Safety (see below).

### 7.4. Deaths and other serious adverse events

#### 7.4.1. Pivotal studies

There were no deaths, SAEs or other significant AEs in any of the three pivotal studies.

#### 7.4.2. Other studies

Not applicable.

### 7.5. Discontinuation due to adverse events

#### 7.5.1. Pivotal studies

There were no discontinuations due to AEs in any of the three pivotal studies.

#### 7.5.2. Other studies

Not applicable.

### 7.6. Laboratory tests

In the three pivotal studies, mean changes from baseline for any parameter were negligible. Most patients had laboratory values within the reference range, or had only transient changes throughout the studies. Values that were normal at baseline but outside the reference range post-baseline were rare and not clinically important.

### 7.7. Liver function

#### 7.7.1. Pivotal studies

There were no clinically important changes in liver function in any of the three pivotal studies.

#### 7.7.2. Other studies

Not applicable.

### 7.8. Kidney function

#### 7.8.1. Pivotal studies

There were no clinically important changes in renal function in any of the three pivotal studies.

#### 7.8.2. Other studies

Not applicable.

## 7.9. Other clinical chemistry

### 7.9.1. Pivotal studies

There were no clinically important changes in clinical chemistry or urinalysis in any of the three pivotal studies.

### 7.9.2. Other studies

Not applicable.

## 7.10. Haematology

### 7.10.1. Pivotal studies

There were no clinically important changes in haematology in any of the three pivotal studies.

### 7.10.2. Other studies

Not applicable.

## 7.11. Electrocardiograph

### 7.11.1. Pivotal studies

No ECGs were performed in any of the three pivotal studies.

## 7.12. Vital signs

### 7.12.1. Pivotal studies

There were no clinically meaningful fluctuations from baseline in SBP, DBP and HR in any of the three pivotal studies.

### 7.12.2. Other studies

Not applicable.

## 7.13. Supportive safety data based on pooled analysis of all GAD clinical studies

To support the current application for the use of GAD in whole body imaging, all clinical studies have been pooled into two Integrated Summary of Safety studies (ISS-1 and ISS-2). ISS-1 includes 15 Phase 1 studies, and ISS-2 includes 38 Phase 2-4 studies (Table 55).

**Table 55: Integrated analysis**

| Phase I and Phase II-IV (all Phases) = 47 studies | | | | | |
|---|---|---|---|---|---|
| **Integrated analysis pool** | **Study phase** | | **Number of studies** | **Subjects enrolled and treated** | **Subject treatments[1]** |
| **Phase I** | All gadobutrol studies | | 9 | 313 | 313 |
| | All placebo-controlled studies (a subset of all Phase I studies) | | 6 | 262 | 262 |
| **Phase II-IV** | **Gadobutrol** | Phase II | 13 | 1345 | 1345 |
| | | Phase III | 23 | 4198 | 4198 |
| | | Phase IV | 2 | 205 | 205 |
| | | **Total** | **38** | **5748** | **5748** |
| | **Gadobutrol or comparators** | Phase II | 13 | 1408 | 1790 |
| | | Phase III | 23 | 5316 | 5782 |
| | | Phase IV | 2 | 209 | 360 |
| | | **Total** | **38** | **6933** | **7932** |

[1] Subjects from crossover studies (studies 308200, 309762, 310123, 310864, and 312021) were analyzed by period. Therefore, the number of analyzed subjects (based on subject treatments) is higher than the number of enrolled subjects.

### 7.13.1. IIS-1

The Phase I studies involving 313 subjects dosed with GAD are listed in Table 56.

**Table 56: Subjects by study for ISS Phase I**

| Study number | Total gadobutrol experience (9 studies, includes all subjects) | Gadobutrol vs. Placebo [a] (6 studies, includes only studies with a placebo arm) | | |
|---|---|---|---|---|
| | Gadobutrol | Gadobutrol | Placebo | Total |
| Total | 313 (100.0%) | 194 (100.0%) | 68 (100.0%) | 262 (100.0%) |
| 91798 | 31 ( 9.9%) | - | - | - |
| 92001 | 40 ( 12.8%) | 40 (20.6%) | 15 ( 22.1%) | 55 ( 21.0%) |
| 92010 | 24 ( 7.7%) | 24 (12.4%) | 12 ( 17.6%) | 36 ( 13.7%) |
| 93016 | 24 ( 7.7%) | 24 (12.4%) | 8 ( 11.8%) | 32 ( 12.2%) |
| 96063 | 20 ( 6.4%) | - | - | - |
| 97113 | 36 ( 11.5%) | 36 (18.6%) | 12 ( 17.6%) | 48 ( 18.3%) |
| 98098 | 45 ( 14.4%) | - | - | - |
| 307362 | 61 ( 19.5%) | 38 (19.6%) | 13 ( 19.1%) | 51 ( 19.5%) |
| 310865 | 32 ( 10.2%) | 32 (16.5%) | 8 ( 11.8%) | 40 ( 15.3%) |

[a] Subject numbers in the gadobutrol column for studies 91798, 96063, and 98098 are not included as these 3 studies did not have a placebo arm

The majority of subjects were male (74.4%) with a mean age of 32.3 and a mean body weight of 72.59 kg. The incidence of AEs was higher in the GAD group (46.9%) compared to the placebo group (29.4%). The most frequently reported AEs in the GAD group were dysgeusia (11.9%), nausea (7.2%), parosmia (6.7%), headache (6.2%), feeling hot (5.2%), and injection site coldness (4.1%). ADRs were reported in 35.6% of the GAD group and in 13.2% of the placebo group. The most common ADRs in the GAD group were dysgeusia (11.9%), parosmia (6.7%), nausea (6.2%), feeling hot (5.2%), and injection site coldness. The most frequently reported AE in the placebo group was injection site coldness (5.9%). In the GAD group, 92.6% of AEs were of mild or moderate intensity, 4.7% were considered severe, and the balance of 2.7% unknown. Of the 337 AEs in the GAD group, 50.1% developed within 30 minutes after the injection. No deaths were reported in ISS-1. There was one SAE in the GAD group (anaphylaxis of moderate severity) compared with none in the placebo group. Two subjects discontinued prematurely due to moderate hypersensitivity reactions. Most subjects had no changes in laboratory parameters after dosing and there were no meaningful differences between the GAD and placebo groups. No clinically significant effects of GAD were detected for SBP, DBP, HR, respiratory rate and body temperature.

### 7.13.2. ISS-2

In the Phase 2-4 studies, AEs were reported in 9.7% of the 5748 patients who received GAD. The only reported AEs with ≥0.5% incidence in the GAD group were headache (1.5%), nausea (1.1%), and dizziness (0.5%). In the comparator groups, the incidences of AEs were 1.9% (Gd-DOTA), 4.7% (gadodiamide), 5.7% (Gd-DTPA), 17.2% (gadoversetamide), and 18.7% (gadoteridol) with no meaningful differences in the respective AE profiles. ADRs were reported by the investigator in 3.5% of patients (Table 57), most commonly nausea (0.7%).

**Table 57: ISS Drug related adverse events with ≥0.5% incidence by system organ class and preferred term in the gadobutrol group-ISS Phase II-IV**

| Primary System Organ Class and Preferred Term | Gadobutrol |
|---|---|
| Number of subjects | 5748 (100.0%) |
| Number of subjects with any AE | 555 ( 9.7%) |
| Number of subjects with any drug related AE | 204 ( 3.5%) |
| Total number of AE | 821 |
| Number of drug related AE | 273 |
| **Gastrointestinal disorders** | |
| Nausea | 39 ( 0.7%) |

The most common ADRs as defined by the sponsor are shown in Table 58.

**Table 58: ISS Adverse drug reactions ISS Phase II-IV**

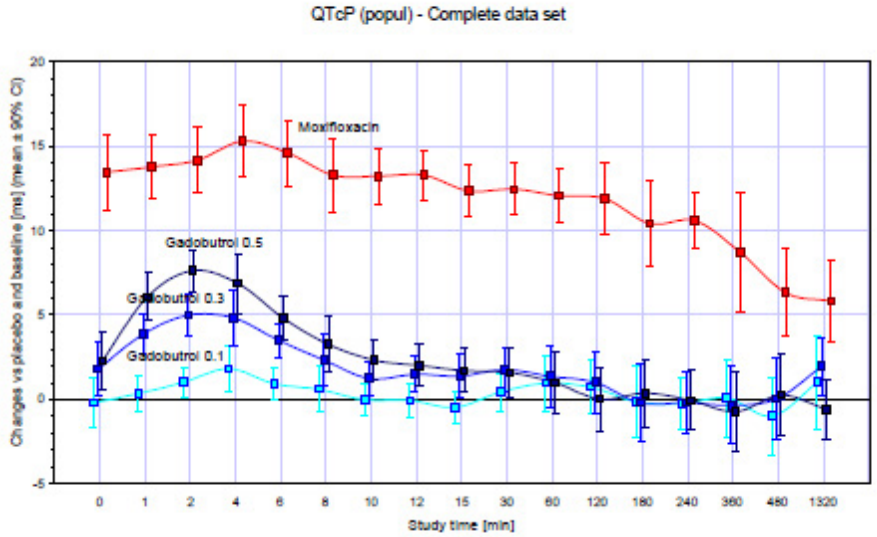
| Adverse drug reaction | Incidence (%) (N = 5748 subjects) |
|---|---|
| Headache | 1.5 |
| Nausea | 1.1 |
| Dizziness | 0.5 |
| Dysgeusia | 0.4 |
| Feeling hot | 0.4 |
| Injection site reaction (various kinds) [a] | 0.3 |
| Vomiting | 0.3 |
| Rash (includes generalized, macular, papular, pruritic rash) | 0.3 |
| Hypersensitivity/anaphylactoid reaction cumulative [b] | 0.2 |
| Pruritus (includes generalized) | 0.2 |
| Erythema | 0.2 |
| Dyspnea | 0.2 |
| Paresthesia | 0.1 |

[a] Injection site reactions (various kinds) comprise the following terms: Injection site extravasation, injection site burning, injection site coldness, injection site warmth, injection site erythema or rash, injection site pain, and injection site hematoma.
[b] Hypersensitivity/anaphylactoid reaction may occur with one or more of the following adverse reactions: e.g. hypotension, urticaria, face edema, eyelid edema, flushing.
Source: Module 5.3.5.3.2, ISS Phase II-IV, based on Table 48 and a causality assessment of the sponsor ; AEs coded by MedDRA, version 14.1

Of the 821 AEs in the GAD group, 76.2%, 19.6% and 4.0% were of mild, moderate and severe intensity, respectively. Most of the AEs (73.1%) were reported within 24 hours and 28.5% were reported within 30 minutes. There were nine discontinuations due to AEs but only three events were considered drug related. There was one death during the course of a study in the GAD group. This was considered due to worsening disease (breast cancer) and unrelated to GAD. Five other patients died after study completion but none was considered related to GAD. Within 72 hours of drug administration, SAEs were reported in 16 (0.3%) patients in the GAD group, compared with one (0.4%) in the gadoversetamide group and three (0.5%) in the gadoteridol group. Only one SAE was considered drug related by the investigator (crystalluria).

There were no clinically important trends or in laboratory parameters after dosing. No clinically significant effects of GAD were detected for SBP, DBP, HR, respiratory rate and body temperature. A Thorough QTc study demonstrated only minor and transient increases in QTc intervals after dosing (Figure 7). The changes were <10 msec for all GAD doses including the supra-maximal dose of 0.5 mmol/kg BW.

**Figure 7: ISS ECG evaluation-Mean differences from placebo and baseline in QTc intervals corrected for QT/RR hysteresis and heart rate based on population optimised models.**



### *Subgroup analyses*

The incidences of AEs and ADRs in subgroups defined by gender, age, body weight, region and race were shown. In the total group, 9.7% of patients reported AEs and 3.5% reported ADRs. In the small number of paediatric patients, the incidence of AEs was higher than in the general population but the incidence of ADRs was similar to the adult population. The reported incidence of AEs was higher in North and South America than other regions. However, there were no meaningful differences between the subgroups and the overall population. There were no difference in the number of AEs or ADRs in patients with or without a history of cardiovascular disorders, and patients with or without hepatic impairment.

### *Hypersensitivity reactions*

In ISS-1, hypersensitivity reactions were reported in 2/313 (0.6%) subjects within 24 hours of dosing, one of which was a SAE of moderate intensity. In ISS-2, 8/5748 (0.1%) patients had hypersensitivity reactions, five of which were mild in intensity.

### *Renal impairment*

In ISS-2, the number of AEs reported in patients categorised by renal function are shown in Table 59. Overall, the incidence of AEs was only marginally higher for patients with renal impairment compared with the total population. The incidence of ADRs in patients with eGFR <30 mL/min was 7.3% compared with 4.8% in patients with normal renal function.

**Table 59: ISS Subjects with adverse events by renal impairment ISS Phase II-IV**

| Renal impairment by eGFR | Gadobutrol – Total 5748 subjects | |
|---|---|---|
| <30 mL/min | No. of subjects | 41 (100.0%) |
| | No. of subjects with any AE | 8 ( 19.5%) |
| | No. of subjects with drug related AE | 3 ( 7.3%) |
| 30 to <60 mL/min | No. of subjects | 416 (100.0%) |
| | No. of subjects with any AE | 34 ( 8.2%) |
| | No. of subjects with drug related AE | 13 ( 3.1%) |
| 60 to <90 mL/min | No. of subjects | 1393 (100.0%) |
| | No. of subjects with any AE | 133 ( 9.5%) |
| | No. of subjects with drug related AE | 53 ( 3.8%) |
| ≥90 mL/min | No. of subjects | 1996 (100.0%) |
| | No. of subjects with any AE | 274 ( 13.7%) |
| | No. of subjects with drug related AE | 96 ( 4.8%) |
| missing | No. of subjects | 1902 (100.0%) |
| | No. of subjects with any AE | 106 ( 5.6%) |
| | No. of subjects with drug related AE | 39 ( 2.1%) |

## 7.14. Post-marketing experience

As of 31 July 2013, the sponsor estimates that more than 15,775,576 patients have received Gadovist® since first launch in Switzerland in 1999. It is now approved in 100 countries and marketed in 68 of these. In that time, Bayer Global Pharmacovigilance (GPV) has received 3,375 ADR reports of which 929 were considered SAEs. The type of ADRs are consistent with those reported in clinical trials, no new safety signals have been identified, and there is no change to the risk/benefit profile of Gadovist®.

### 7.14.1. Deaths

There have been 36 deaths (18 females, 16 males, 2 gender unreported) in patients aged 31 to 91 years, occurring on the same day or up to 22 months following drug injection. The cause of death was considered to be secondary to anaphylactic reactions in 17 of these deaths although the diagnosis was not completely clear in four of these cases. Two spontaneous reports were non-assessable. In the remaining 11 cases, the cause of death included metastatic disease, tumour progression, complications of underlying cancer, advanced cardiac disease, GI bleeding, lung bleeding, liver failure with sepsis, and multi-organ failure associated with bowel infarction. Three deaths were reported in patients with NSF but none were considered related to GAD. The

incidence of fatalities associated with GAD is 0.12 per 100,000 patients which is consistent with other marketed Gd-containing contrast agents.

### 7.14.2. Hypersensitivity reactions

Hypersensitivity reactions include the cardiovascular, respiratory and cutaneous symptoms listed. Reactions were reported in approximately 0.01% of the 15,775,576 million drug administrations and most were mild to moderate in intensity. The frequency of hypersensitivity reactions is similar to other Gd-containing contrast agents.

### 7.14.3. Nephrogenic systemic fibrosis

There have been 11 cases of NSF known to the sponsor during the reporting period, four of which are considered by the sponsor to be causally related to GAD. At FDA request, the sponsor joined the GRIP study which started in 2008 and is still ongoing. The GRIP study is a prospective study of all Gd-containing contrast agents with the objective of monitoring NSF rates for up to 24 months post-dose. A total of 928 GAD patients have been recruited but no cases of NSF have been reported at the April 2013 cut-off (Table 60).

**Table 60: PMS data Study status by patient cohort s and by follow-up visits completed**

| Number of patients in Follow-up (as of DLP) | | | Number of patients – Follow-up visits completed | | | | | |
|---|---|---|---|---|---|---|---|---|
| Moderate renal impairment | Severe renal impairment | eGFR 60-65 | 1 month | 3 months | 6 months | 12 months | 18 months | 24 months |
| 240 | 106 | 14 | 796 | 742 | 660 | 466 | 383 | 292 |
| Numbers from status report as of 15 Apr 2013 | | | | | | | | |

### 7.14.4. Literature review

The literature review of the use of GAD, MAG and DOT in body areas and organs offered little additional safety information. Overall, adverse events in articles which met the review criteria were under-reported, selectively reported or not reported at all. These sparse data cannot be usefully evaluated. However, the prevalence of acute ADRs related to GAD in 14,299 participants of studies conducted by the sponsor was published in 2010 (Ref 1). A total of 128 ADRs were reported in 78 (0.55%) patients and no individual ADR reached a frequency of 1%. The most ADRs were nausea (0.25%), vomiting (0.05%) and urticaria (0.04%). Feelings of warmth, tachycardia, and wheals were each reported in 0.03% of patients; dizziness, itching, vasodilatation, and itchy throat were each reported in 0.02% of patients; and cough, dyspnoea, flushing, hives, generalised itching, oral dryness, facial redness, sensation of heat, skin disorders, and aggravated nausea were each reported in 0.01% of patients. The frequency and pattern of ADRs was compatible with data in the PI.

## 7.15. Safety issues with the potential for major regulatory impact

### 7.15.1. Liver toxicity

No issues identified.

### 7.15.2. Haematological toxicity

No issues identified.

### 7.15.3. Serious skin reactions

No new issues identified.

### 7.15.4. Cardiovascular safety

No issues identified.

#### 7.15.5. Unwanted immunological events

No new issues identified. There is a small but significant risk of hypersensitivity reactions including anaphylaxis and death.

### 7.16. Other safety issues

#### 7.16.1. Safety in special populations

13297: AEs were more frequent in Asian males (4.8%) than Asian females (3.2%). There were no age related differences in AEs.

#### 7.16.2. Safety related to drug-drug interactions and other interactions

Not applicable.

### 7.17. Evaluator's overall conclusions on clinical safety

Clinical trial and updated PMS data have identified no new safety concerns for Gadovist®. The frequencies of the known adverse events (mostly minor) have changed only marginally. Most individual ADRs remain uncommon, reported in ≤0.5% of patients. The safety section of the approved PI has been updated to reflect these changes but the overall safety profile remains unchanged and consistent with other gadolinium-containing contrast agents.

# 8. First round benefit-risk assessment

### 8.1. First round assessment of benefits

The benefits of Gadovist® in the proposed usage are:

- Improved imaging performance compared with unenhanced MRI for whole body imaging, in particular for the detection and assessment of malignancies.
- High accuracy in the diagnosis and assessment of cardiac pathology, in particular coronary artery disease.
- Predictable diagnostic accuracy comparable with other gadolinium-based contrast agents in the class.

### 8.2. First round assessment of risks

The risks of Gadovist® in the proposed usage are:

- Hypersensitivity reactions, mostly mild but potentially causing death.
- Rare cases of nephrogenic systemic fibrosis.

### 8.3. First round assessment of benefit-risk balance

CE-MRI is a gold standard whole body imaging technique with particular value in the detection, staging and follow-up of malignancies. It is an important tool in the investigation of breast cancers when used in combination with XRM. It is also very accurate in the assessment of cardiac conditions including coronary artery disease. With approval of the new indications, the benefits of GAD will match those of other agents in the class including MAG and DOT. The risk profile remains favourable, although the frequency of ADRs will increase numerically with wider use. The benefit-risk balance of Gadovist®, given the proposed usage, is unchanged and favourable.

### 8.4. First round recommendation regarding authorisation

Authorisation of Gadovist® is recommended for the additional indications of:

- Contrast enhancement in whole body MRI including head and neck region, thoracic space, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus), retroperitoneal space (kidney), extremities and musculoskeletal system.
- Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.

# 9. Clinical questions

No questions were raised.

# 10. Second round evaluation of clinical data submitted in response to questions

No second round evaluation was required.

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**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au  Phone: 1800 020 653  Fax: 02 6232 8605
**https://www.tga.gov.au**