An open label, multi-center, phase 3 study with corresponding blinded image reading to determine the efficacy and safety of a single intravenous injection of 0.1 mmol/kg body weight of gadobutrol 1.0 molar (GadovistÂ®) in patients with newly diagnosed breast cancer referred for contrast-enhanced breast MRI

Published: 05-02-2010
Last updated: 02-05-2024

To assess the effectivity and safety of 1.0 molar gadobutrol (Gadovist®) for breast MRI

Ethical review	Approved WMO
Status	Pending
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON35053

Source
ToetsingOnline

Brief title
Efficacy and safety of gadobutrol 1.0 molar (Gadovist®) for breast MRI

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, mammacarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: farmaceutisch bedrijf

Intervention

Keyword: efficacy, Gadovist, MRI, safety

Outcome measures

Primary outcome

The primary objectives of this study are to demonstrate:

1. Superiority of combined unenhanced and gadobutrol-enhanced breast MRI (MR Mammography; MRM) versus unenhanced MRM

2. Superiority of combined unenhanced and gadobutrol-enhanced MRM plus X-ray mammography (XRM) versus unenhanced MRM plus XRM

Based on categorical accuracy for malignant breast disease on breast region level with 3 categories (unifocal, multifocal malignant disease or no malignant disease present) and verified by the predefined Standard of Truth (SoT; histopathology or alternatively XRM plus ultrasound.

The evaluation of the breast will be performed by regions (5 regions per each breast: 4 quadrants and the central region including the nipple). For each breast region the reader will choose the category which best describes the extent of malignant disease:

1 2 3

None Unifocal disease Multifocal disease

The value of the primary efficacy variable will be determined for all breast regions by whether or not the category chosen by the imaging modality matches the disease state (no disease, unifocal or multifocal disease) determined by the SoT. The proportion of correct matches will be used to measure categorical accuracy. Statistical analysis of this variable will be performed using techniques which take into account the multiple assessments per patient.

Secondary outcome

The secondary objectives of this study are to evaluate:

1. Combined unenhanced and gadobutrol-enhanced MRM versus unenhanced MRM

2. Combined unenhanced and gadobutrol-enhanced MRM plus XRM versus unenhanced MRM plus XRM

3. Combined unenhanced and gadobutrol-enhanced MRM plus XRM versus XRM alone

Based on:

• Categorical accuracy by descriptive statistics using breast regions with SoT based on histology only

• Sensitivity and specificity for malignant breast disease on breast region level for disease / no disease

• Sensitivity and specificity for unifocal malignant breast disease on breast region level for unifocal disease / no unifocal disease

• Sensitivity and specificity for multifocal malignant breast disease on breast region level for multifocal disease / no multifocal disease

• Accuracy of the presence of the multicentric malignant disease *Yes/No* per

breast

• Accuracy of the presence of bilateral malignant disease *Yes/No* per patient

• Confidence in diagnosis on breast region level

In addition, combined unenhanced and gadobutrol-enhanced MRM plus X-ray mammography (XRM) versus XRM alone will be also evaluated for the:

• Categorical accuracy in determination of the extent of malignant breast disease on breast region level with 3 categories (unifocal, multifocal malignant disease or no malignant disease present)

The extent of malignant breast disease will be determined for each breast region. The disease states *multicentric malignant disease* and *bilateral malignant disease* will be derived from the assessment of the different regions for each breast (right and left) per patient.

All primary and secondary objectives will be evaluated for the investigators as well as for the blinded readers.

To assess the safety of gadobutrol after intravenous (i.v.) administration in this study.

As secondary analyses, descriptive statistics will be provided for the comparisons of categorical accuracy in the determination of malignant breast disease based on regions verified by histopathology and sensitivity and specificity of the detection/exclusion of:

malignancy in a breast region;

* unifocal disease in a breast region;

* multifocal disease in a breast region;

will also be calculated.

Accuracy of the presence of multicentric malignant disease and bilateral malignant disease will be derived from assessment of the different regions per breast and per patient, respectively.

The same evaluations (i.e. categorical accuracy, sensitivity and specificity, multicentric malignant disease and bilateral malignant disease) will be performed for the combined unenhanced and gadobutrol-enhanced MRM versus unenhanced MRM, for combined unenhanced and gadobutrol-enhanced MRM plus XRM versus unenhanced MRM plus XRM, and for the combined unenhanced and gadobutrol-enhanced MRM plus XRM versus XRM alone.

Confidence in diagnosis will be evaluated for all comparisons described above.

Study description

Background summary

Breast cancer is the most commonly detected non-skin cancer among women in the developed world. About one third of women die of the disease, although it is curable when detected early. A multidisciplinary approach is required in order to ascertain early diagnosis of the tumor extent and optimum treatment to reduce morbidity and mortality. Most primary breast cancers are detected by clinical breast examination and routine X-ray mammography (XRM), which is the screening method for the detection and localization of breast anomalies. In order to overcome some diagnostic limitations of XRM (overlap of tissue densities and limited contrast between malignant and benign tissues), other non-invasive diagnostic imaging methods like ultrasound and magnetic resonance imaging (MRI) of the breast have been employed to provide complementary information. Contrast agents like Gadovist are used to enhance the anomalies.

Study objective

To assess the effectivity and safety of 1.0 molar gadobutrol (Gadovist®) for

breast MRI

Study design

The results of he MRI images after the Gadovist injection, will be compared wit the MRI images without Gadovist and the images of the XRM that was taken earlier. The results of the planned breast surgery that will be performed after the study will be used as evaluation standard.

Intervention

All enrolled patients will receive Gadovist.

Study burden and risks

burden for the patient:
1 MRI with Gadovist (MRI exam with comparable contrast agent was already planned)
1 additional visit (follow-up visit)
1 physical examination, 2 short check-ups
possibly an additional ultrasound

Risk:
the patient is already scheduled for a MRI with another gadolidium containing contrast agent. the possible adverse events of the routinely used contrast agent and the investigational product are comparable. the reported adverse events occur most frequently within one hour after administration. during this time the patient is onder supervision of a physician.

Safety data from preclinical and clinical development, from postmarketing surveillance of Gadovist, as well as from published data with Gadovist support the expectation of a safe use in the selected patient population. Exclusion criteria, in particular with regard to renal insufficiency and potential effects on QT interval, were selected to maximize safety and patient protection in this study.
The overall risk-benefit ratio is regarded as favorable and comparable to all other marketed ECCMs and there are no objections from a preclinical or clinical point of view against the proposed trial in the patient population.

Contacts

Public
Bayer

Kaiser-Wilhelm-Allee
AG D-51368 Leverkusen
DE
Scientific
Bayer

Kaiser-Wilhelm-Allee
AG D-51368 Leverkusen
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Is at least 18 years of age.
2. Has recent histologically proven diagnosis of breast cancer after having obtained XRM of both breasts (according to American College of Radiology [ACR] and performed no longer than 6 weeks prior to enrollment into the study) and has been referred for a contrast-enhanced MRM prior to surgery of the breast.
3. If female, a digital XRM is required if any of the following criteria is met:
a. Patient is younger than 50 years;
b. Patient has heterogeneously or extremely dense breasts (based on the quantitative criteria for the BI-RADS mammographic density categories of 51%-75% for heterogeneously dense, and >75% dense for the extremely dense category);
c. Is not post-menopausal (post-menopause defined as at least 12 months prior to inclusion without menstruation).
4. Is willing to undergo the contrast-enhanced MRM examinations with gadobutrol.
5. Is willing and able to complete all study procedures specified in the protocol.
6. If female, patient is either not of childbearing potential, or is female of childbearing potential who is using any medically accepted means of contraception and has a negative urine pregnancy test within 1 hour prior to the administration of gadobutrol.
7. If female of childbearing potential, MRM should be performed on the 7-14th day of the

menstrual cycle.
8. Has an estimated glomerular filtration rate (eGFR) value >= 60 mL/min/1.73m2 derived from a serum creatinine result within 2 weeks prior to study enrollment.

Exclusion criteria

1. Is a female patient who is pregnant or lactating.
2. Has received any investigational product or has participated in any other clinical trial within 30 days prior to enrolling in this study.
3. Has been previously enrolled in this study.
4. Has any contraindication to the MRM examination (e.g. metal implants, phobia) or the use of gadolinium-containing contrast agents.
5. Has a history of severe allergic or anaphylactoid reaction to any allergen including drugs and contrast agents.
6. Has received any contrast agent within 24 hours prior to the study MRM, or is scheduled to receive any contrast agent within 24 hours after the study MRM.
7. Is considered clinically unstable or his/her clinical course during the study period is unpredictable (e.g., due to previous surgery, acute renal failure).
8. Has severe cardiovascular disease (e.g., known long QT syndrome, acute myocardial infarction [< 14 days], unstable angina, congestive heart failure New York Heart Association class IV) or acute stroke (< 48 hours)).
9. Has acute renal insufficiency of any severity due to hepato-renal syndrome or in the peri-operative liver transplantation period or who has acute or chronic moderate or severe renal insufficiency (glomerular filtration rate < 60 mL/min/1.73m2).
10. Has received chemotherapy or hormonal therapy for breast cancer within 6 months.
11. Has received hormone replacement therapy within 4 weeks prior to study drug administration.
12. Is scheduled or likely to require a surgery and/or biopsy in the time period up to 24 hours following study drug application
13. Has prior excisional biopsy or breast surgery less than 6 months before enrollment and between XRM and study MRM

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-03-2010
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Gadovist
Generic name:	gadobutrol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-02-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-08-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-009598-90-NL
CCMO	NL30925.091.10