Clinical Study Report Synopsis **GE Healthcare**
SOV302

Title: A Multicenter, Phase 3, Open-Label Study to Assess the Efficacy and Safety of 0.1 mmol/kg OMNISCAN™ (Gadodiamide Injection) for Magnetic Resonance Angiography (MRA) of the Aorto-iliac Arteries.

This is an exact copy of the synopsis from the final clinical study report for the study SOV302. The final clinical study report (document-identifier: CC SOV302 CSR) was authorized for use on 06 March 2009 (Version 3.0).

SYNOPSIS

Name of Sponsor/Company: GE Healthcare **Name of Finished Product:** OMNISCAN™ **Name of Active Ingredient:** Gadodiamide (Gd-DTPA-BMA)	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:** **Volume:** **Reference:**	**(For National Authority Use only)**
Title of Study: A Multicenter, Phase 3, Open-Label Study to Assess the Efficacy and Safety of 0.1 mmol/kg OMNISCAN™ (Gadodiamide Injection) for Magnetic Resonance Angiography (MRA) of the Aorto-iliac Arteries.		
Investigators and Study Center(s): A total of 40 study centers, 24 in Europe and 16 in North America, enrolled a total of 407 subjects in this study.		
Investigator(s) and Centers for Independent Evaluation of Images: The blinded image evaluation (BIE) was performed at the independent Image Review Center (IRC) in Oslo, Norway.		
Publication (reference): Not applicable		
Study Period: 28 September 2004 to 28 February 2006	**Phase of Development:** 3	

Objectives:

Primary Objective:

To determine the efficacy of 0.1 mmol/kg OMNISCAN for three-dimensional contrast-enhanced (3D CE) MRA (hereinafter referred to as "OMNISCAN MRA") compared to 2-dimensional time-of-flight (2D TOF) MRA (hereinafter referred to as "non-contrast MRA") in identification of the presence or absence of hemodynamically relevant stenoses (i.e. ≥50% or occlusion) within turbulent flow arteries of the aorto-iliac region. Intra-arterial digital subtraction angiography (IA DSA) was used as the standard of truth (SOT).

Secondary Objectives:

- To determine the efficacy of 0.1 mmol/kg OMNISCAN for 3D CE MRA compared to non-contrast MRA in the identification of the presence or absence of the hemodynamically relevant stenosis on a segment to segment level within any of the 7 aorto-iliac arterial segments. IA DSA was used as the SOT.
- To evaluate the impact of OMNISCAN MRA findings compared to those of non-contrast MRA and IA DSA on overall clinical utility on the basis of the consensus decision of a vascular surgeon and a radiologist as to: the occlusion or stenosis requiring the most radical treatment and the recommendation of the most appropriate revascularization strategy for the lesion (i.e. endovascular intervention combined with vascular surgery, vascular reconstructive surgery, endovascular intervention, no revascularization possible, no revascularization necessary).
- To evaluate the safety of OMNISCAN injection via a power injector in subjects who received a dose of 0.1 mmol/kg or a dose exceeding 0.1 mmol/kg.

Study Design: This was a multicenter, Phase 3, open-label study to assess the efficacy and safety of OMNISCAN for OMNISCAN MRA in the identification of the presence or absence of hemodynamically relevant stenoses in turbulent flow arteries of the aorto-iliac region in subjects with suspected or proven peripheral arterial occlusive disease (PAOD) and to assess the overall efficacy in the grading of hemodynamically relevant stenoses/occlusions on a segment to segment level.

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Selection of Subjects: Subjects with chronic PAOD predominantly located in the aorto-iliac region with Fontaine Stages IIb to IV (Rutherford Stages I_3-III) or presenting with an ankle brachial pressure index of <0.70 (measured no more than 3 months prior to screening) were included in the study.

Main inclusion criteria:

- The subject was 18 years or older.
- The subject had suspected or proven chronic PAOD predominantly located in the aorto-iliac region with Fontaine Stages IIb to IV (Rutherford Stages I_3-III), or presenting with an ankle brachial pressure index of <0.70 (measured no more than 3 months prior to screening).
- The subject had been referred to IA DSA for determination of subject management (no more than 1 month prior to inclusion).
- The subject had no intervention or change of symptoms within the region of interest (ROI) between OMNISCAN MRA and IA DSA.

Number of Subjects (planned and analyzed): A total of 295 subjects were planned to achieve a sample size of 193 subjects evaluable for sensitivity and 193 segments evaluable for specificity. However, to include sufficient number of subjects with hemodynamically relevant stenosis, a total of 407 subjects (221 in Europe and 186 in North America) were enrolled. Of these, 401 subjects were included in the safety analysis and 333 subjects were included in the ITD efficacy analysis.

Treatment of Subjects

Investigational Medicinal Product (IMP): OMNISCAN was administered via a power injector as a single intravenous bolus injection at a dose of 0.1 mmol/kg. Further injection(s) of study drug (up to a maximum additional dose of 0.2 mmol/kg, using a power injector) for imaging more distal regions of the leg, if needed for clinical decision making, were left to the discretion of the on-site Investigator. The maximum total dose allowed of 0.3 mmol/kg OMNISCAN (including the first injection of 0.1 mmol/kg OMNISCAN for imaging the aorto-iliac region) was not to be exceeded.

Comparator: non-contrast (2D TOF) MRA.

Standard of Truth: non-selective IA DSA (read by 2 blinded IA DSA readers independently and afterwards in consensus).

Duration of Treatment: Each subject participated in the study for approximately 27 hrs (including a safety assessment from within 3 hrs prior to OMNISCAN injection through a 24-hr safety follow-up).

Endpoints

Efficacy:

Co-primary efficacy endpoints:

The following primary efficacy endpoints were evaluated simultaneously for each MRA reader:

(1) Difference in sensitivity between OMNISCAN MRA and non-contrast MRA in identification of the hemodynamically relevant stenosis at the subject level across the 7 aorto-iliac arterial segments with IA DSA as the SOT.

The hemodynamically relevant stenosis was defined as the stenosis with the highest grade (i.e. percentage decrease in vessel diameter) in 1 of the 7 segments as determined by the IA DSA consensus.

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(2) Difference in specificity between OMNISCAN MRA and non-contrast MRA in identification of a hemodynamically relevant stenosis based on all of the 7 aorto-iliac arterial segments combined with IA DSA as the SOT. All segments across all subjects, which were determined to have no hemodynamically relevant stenosis by the IA DSA BIE were considered for the calculation of specificity.

The results of 3 independent blinded MRA readers were compared separately to the IA DSA findings in each subject.

Secondary efficacy endpoints:

A. Difference in specificity and accuracy between OMNISCAN MRA and non-contrast MRA in identification of the hemodynamically relevant stenosis at the subject level across the 7 aorto-iliac arterial segments with IA DSA as the SOT.
B. Difference in sensitivity and accuracy between OMNISCAN MRA and non-contrast MRA in identification of a hemodynamically relevant stenosis based on all 7 aorto-iliac arterial segments combined with IA DSA as the SOT.
C. Sensitivity and specificity of OMNISCAN MRA versus non-contrast MRA in identification of a hemodynamically relevant stenosis on a segment to segment level for each of the 7 aorto-iliac arterial segments separately with IA DSA as the SOT.
D. Image quality and number of segments evaluable in the aorto-iliac region of OMNISCAN MRA and non-contrast MRA compared with IA DSA.
E. A majority decision analysis was conducted for the co-primary endpoints and the secondary endpoints A and B to combine all reads in a single analysis.
F. Sensitivity and specificity of OMNISCAN MRA versus non-contrast MRA in identification of an occlusion at the subject level across the 7 aorto-iliac arterial segments with IA DSA as the SOT.
G. Consensus assessment of a vascular surgeon and a radiologist to determine the occlusion or stenosis requiring the most radical treatment (i.e. vascular surgery combined with endovascular intervention, vascular reconstructive surgery, endovascular intervention, no revascularization possible, no revascularization necessary) and the recommendation of the most appropriate revascularization strategy for that lesion based on OMNISCAN MRA, non-contrast MRA, and IA DSA within the aorto-iliac regions.

Secondary efficacy endpoints A to D and F were analyzed for each of the 3 independent blinded MRA readers separately. Secondary efficacy endpoint G was analyzed as the consensus assessment of a vascular surgeon and a radiologist. The 3 imaging procedures (OMNISCAN MRA, non-contrast MRA, and IA DSA) of the same subject were evaluated separately.

Safety:

- Adverse events (AEs) were assessed for occurrence, relationship to OMNISCAN, severity, and seriousness throughout the study duration up to 24 hrs after contrast injection.
- Limited physical examination, vital signs, 12-lead ECGs, injection site monitoring, and laboratory parameters were performed at predetermined intervals from baseline to the end of the study.
- The safety of OMNISCAN injection via a power injector was assessed by an evaluation of injection site reactions and a determination of whether the type and frequency of injection site reactions correlated with injection rates.

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Statistical Analyses

The differences in sensitivity (subject level) and specificity (vessel level) between OMNISCAN MRA and non-contrast MRA were compared for superiority.

The hypotheses were:

H_0: $Sens_{CE} \leq Sens_{TOF}$ versus the alternative hypothesis H_1: $Sens_{CE} > Sens_{TOF}$ and

H_0: $Spec_{CE} \leq Spec_{TOF}$ versus the alternative hypothesis H_1: $Spec_{CE} > Spec_{TOF}$

in which Sens and Spec (sensitivity and specificity) were tested for each MRA reader separately using a 1-sided exact McNemar's test to show superiority of OMNISCAN MRA to non-contrast MRA.

The diagnostic performance of OMNISCAN MRA and non-contrast MRA was also compared to IA DSA at pre-specified threshold values of 70% for both sensitivity and specificity in this study.

Summary of Results

Efficacy Results:

- In the primary analysis based on the PP population, although the numerical sensitivities for all 3 blinded readers were better for OMNISCAN MRA, only 1 reader achieved statistically significant superiority over non-contrast MRA. The difference in specificity between OMNISCAN MRA and non-contrast MRA at the vessel level was statistically significant for 2 of the 3 BIE Readers. The study did not meet both of its pre-specified co-primary efficacy endpoints.
- In the ITD population analysis, the differences between OMNISCAN MRA and non-contrast MRA were statistically significant for 2 of the 3 blinded readers, the majority reader decision for sensitivity, and in all 3 blinded readers for specificity.
- A FDA-requested post-hoc analysis of the co-primary efficacy endpoint using the PP population criteria from companion study SOV301demonstrated results consistent with the ITD analysis.
- A subset analysis of the subjects whose non-contrast MRA images were classified as un-interpretable but whose OMNISCAN MRA images were classified as interpretable by blinded readers achieved statistically significant superiority at the pre-specified threshold value of 60% for specificity.
- In comparison with IA DSA, the sensitivity of OMNISCAN MRA ranged from 80% to 88% and specificity ranged from 71% to 89% at the subject level in the PP analysis, which achieved statistical significance at the prespecified threshold of 70% for all 3 blinded readers for sensitivity and for 2 of the 3 readers for specificity. Similarly, statistical significance was achieved for 2 of the 3 readers for sensitivity and all 3 readers for specificity at the vessel level. The results from the ITD analyses at the subject and vessel levels were similar. In contrast, the sensitivity and specificity of non-contrast MRA did not achieve statistical significance at the minimum threshold of 70% by at least 2 or more blinded readers in any of these analyses (subject or vessel level; PP or ITD analyses).
- The inter-reader agreement (Cohen's κ) at the subject level among the MRA Readers ranged between 0.63 and 0.74 for OMNISCAN MRA and between 0.64 and 0.69 for non-contrast MRA imaging.
- Administration of OMNISCAN for CE MRA substantially reduced MRA imaging time. Image quality was consistently better, according to blinded readers' evaluation, for the OMNISCAN MRA than for non-contrast MRA.

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Safety Results:

- OMNISCAN was well tolerated in subjects with suspected or proven chronic PAOD predominantly located in the aorto-iliac region, consistent with the safety profile in the current package insert.
- Among the 401 subjects who received OMNISCAN, 41 subjects (10%) experienced a total of 48 AEs. Of these subjects, 3 subjects (<1%, 3 AEs) experienced AEs (diarrhea NOS, nausea, and injection site dermatitis) that were considered by the Investigator to be related to OMNISCAN. Thirty-five subjects (9%, 41 AEs) experienced AEs that were mild in intensity. Two (<1%) subjects experienced 1 AE each that were categorized as severe and 1 of which (nausea) was considered related to OMNISCAN by the investigator.
- One subject experienced a fatal SAE (myocardial infarction), which was not considered to be related to OMNISCAN injection.
- Overall, the most commonly reported AEs were injection site hemorrhage (4% of subjects) and injection site bruising (1% of subjects). All other AEs were reported by <1% of subjects.
- The number of subjects with injection site-related AEs was attributed to and consistent with the route of administration (venous puncture) and/or use of a power injector but was not considered the result of an OMNISCAN-related sensitivity reaction.
- Clinical laboratory parameters (serum chemistry and hematology), vital sign measurements (systolic and diastolic BP, HR, and respiration rate) and physician examination generally remained within normal limits following OMNISCAN administration through the 24-hour follow-up. One vital signs result (systolic hypertension) was reported as an AE and 1 subject's physical examination shifted from "normal" to "abnormal" for lungs was considered as an AE (dyspnea NOS). However, no clinically significant changes were evident following administration of OMNISCAN. No clinically significant trends or safety signals were noted.
- ECG interval measurements (PR, RR, QRS, QT and QTc intervals) remained stable over time in nearly all subjects. None of the observed ECG waveform abnormalities were accompanied by changes in subject management.

Conclusions:

OMNISCAN MRA at a dose of 0.1 mmol/kg provided imaging information on aorto-iliac arterial stenoses that compared very favorably with the SOT, IA DSA, used in this study. Non-contrast MRA, as conducted in this study, was also effective. Evaluation of the total efficacy package, however, leads us to conclude that OMNISCAN MRA is better than non-contrast MRA for evaluation of \aorto-iliac stenoses. In addition, OMNISCAN MRA is associated with advantages over non-contrast MRA in terms of image acquisition time and image quality that could translate to clinical benefit.

The safety profile for OMNISCAN demonstrated in this study was very good. There were no trends for safety concerns and most of the AEs were considered to be unrelated to OMNISCAN administration, including the 2 SAEs. In general the safety data generated in the present study are in accordance with those observed for OMNISCAN up to present and demonstrate OMNISCAN to be safe and well tolerated at the dose administered.

In conclusion OMNISCAN was a safe and effective agent for CE MR imaging in the detection of hemodynamically significant stenoses in the aorta-iliac arteries, vessels exhibiting turbulent flow characteristics.