Clinical Study Report Synopsis **GE Healthcare**
SOV301

Title: Phase 3, Open-Label, Controlled Study Evaluating the Efficacy and Safety of 0.1 mmol/kg OMNISCAN™ (Gadodiamide Injection) in Magnetic Resonance Angiography (MRA) of the Renal Arteries.

This is an exact copy of the synopsis from the final clinical study report for the study SOV301. The final clinical study report (document-identifier: CC SOV301 CSR) was authorized for use on 06 March 2009 (Version 3.0).

SYNOPSIS

Name of Sponsor/Company: GE Healthcare	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:**	**(For National Authority Use only)**
Name of Finished Product: OMNISCAN™ (Gadodiamide Injection)		
Name of Active Ingredient: Gadodiamide GdDTPA-BMA	**Volume:**	
	Reference:	
Title of Study: A Multicenter, Phase 3, Open-Label, Controlled Study Evaluating the Efficacy and Safety of 0.1 mmol/kg OMNISCAN™ (Gadodiamide Injection) in Magnetic Resonance Angiography (MRA) of the Renal Arteries.		
Investigators and Study Centers: A total of 39 centers, 19 centers in Western Europe, 12 centers in Eastern Europe (including Turkey), 5 centers in the United States, and 3 centers in South America, enrolled a total of 395 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: 11 September 2003 to 01 August 2005	**Phase of Development:** 3	

Objectives:

Primary Objective:

To confirm the efficacy of 0.1 mmol/kg OMNISCAN for three-dimensional contrast-enhanced (3D CE) MRA (hereinafter referred to as "OMNISCAN MRA") in determining the presence or absence of the main hemodynamically relevant stenosis (i.e. ≥50% or occlusion) at the subject level across both major renal arteries. Intra-arterial digital subtraction angiography (IA DSA) was used as the standard of truth (SOT).

Secondary Objectives:

For secondary efficacy objectives (a) through (h), IA DSA was used as the SOT.

(a) To assess the efficacy and the impact on making a diagnosis of OMNISCAN MRA and two-dimensional time-of-flight (2D TOF) MRA (hereinafter referred to as "non-contrast MRA") in regions predisposed to turbulent flow (i.e. presence/absence of signal loss at the aorto-renal bifurcations as well as length and degree of stenoses of each major renal artery);

(b) To determine the efficacy of non-contrast MRA in determining the presence or absence of the hemodynamically relevant stenosis (i.e. ≥50% or occlusion) at the subject level across both major renal arteries with IA DSA as the SOT and compared with OMNISCAN MRA;

(c) To determine the efficacy of OMNISCAN MRA and non-contrast MRA in determining the presence or absence of the hemodynamically relevant stenosis at the subject level across both major renal arteries with IA DSA as the SOT based on a majority decision analysis;

d) To assess the efficacy of OMNISCAN MRA and non-contrast MRA in determining the presence or absence of hemodynamically relevant stenoses at the vessel level (i.e. within each of the major renal arteries);

(e) To assess the efficacy of OMNISCAN MRA and non-contrast MRA in the combined determination of the presence or absence of hemodynamically relevant stenoses in each of the 2 major renal arteries;

(f) To evaluate the impact of OMNISCAN MRA findings compared to those of IA DSA and non-contrast MRA on the overall clinical usefulness based on the confidence of diagnosis (COD) in determining the most appropriate revascularization strategy;

(g) To compare OMNISCAN MRA with non-contrast MRA in the detection of accessory renal arteries;

(h) To describe image quality and number of segments evaluable in the renal region for each modality.

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Objectives (cont'd):

Safety objective:

To evaluate the safety of OMNISCAN administration in renal MRA via power injector in subjects who received a dose of 0.1 mmol/kg OMNISCAN.

Study Design:

This was a multicenter, Phase 3, open-label study to assess the sensitivity and specificity of OMNISCAN MRA for the detection of renal artery stenoses (RAS) (≥50% or occlusion) with 0.1 mmol/kg OMNISCAN and to assess the efficacy and the impact on making a diagnosis of both OMNISCAN MRA and non-contrast MRA in regions predisposed to turbulent flow. Subjects with a clinical suspicion of or known RAS and referred for IA DSA of this region were evaluated. The subjects underwent non-contrast MRA and OMNISCAN MRA, the results of which were compared with IA DSA as the SOT. The efficacy assessments were based on the independent blinded evaluation of the MRA and IA DSA images by 3 and 2 readers, respectively.

Selection of Subjects: Subjects with suspected or known RAS and referred to the study center for IA DSA, and who fulfilled all of the inclusion and none of the exclusion criteria, were recruited for the study.

Main inclusion criteria:

- The subject was 18 years or older;
- The subject had suspected or known RAS;
- The subject had been referred for IA DSA;
- The subject had had no intervention or change of symptoms between OMNISCAN MRA and IA DSA.

Number of Subjects (planned and analyzed):

A total of 270 subjects were planned to be enrolled to achieve a sample size of 139 subjects evaluable for sensitivity and 106 subjects evaluable for specificity. To achieve an adequate sample size for the primary efficacy analysis a reassessment of power calculation assumptions was performed after the initial blinded read sessions and the study recruitment was extended. A total of 395 subjects were enrolled into the study. Of these, 393 subjects were included in the safety analyses and 335 subjects were included in the efficacy analyses.

Treatment of Subjects:

Investigational Medicinal Product: OMNISCAN was administered via a power injector as a single intravenous bolus injection at a dose of 0.1 mmol/kg.

Comparator: non-contrast (2D TOF) MRA

Standard of Truth: IA DSA

Duration of Treatment: Each subject participated in the study for 24 hours with an additional follow-up contact (usually by telephone) at 72 hours.

Endpoints

Efficacy

Primary endpoints: The primary endpoints were the sensitivity and specificity of OMNISCAN MRA for the detection of the main hemodynamically relevant stenosis across both major renal arteries at the subject level when compared to that of the SOT (IA DSA).

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Endpoints (cont'd):

Secondary Endpoints:

(a) Detection of signal loss in regions predisposed to turbulent flow based on:
- Comparison of OMNISCAN MRA and non-contrast MRA in detecting the presence or absence of signal loss at the aorto-renal bifurcation and the impact on making a diagnosis;
- Comparison of OMNISCAN MRA and non-contrast MRA with the SOT (IA DSA) in determining the length of stenosis and degree of stenosis for each major renal artery at the vessel level.

(b) Accuracy, positive predictive value (PPV) and negative predictive value (NPV) of OMNISCAN MRA in detecting the main hemodynamically relevant stenosis at the subject level across both major renal arteries.

(c) Sensitivity, specificity, accuracy, PPV, and NPV of non-contrast MRA and differences between OMNISCAN MRA and non-contrast MRA in determining the main hemodynamically relevant stenosis at the subject level across both major renal arteries.

(d) Sensitivity, specificity, accuracy, PPV, and NPV of OMNISCAN MRA and non-contrast MRA and differences between OMNISCAN MRA and non-contrast MRA in detecting the main hemodynamically relevant stenosis at the subject level across both major renal arteries based on a majority decision analysis.

(e) Sensitivity, specificity, accuracy, PPV, and NPV of OMNISCAN MRA and non-contrast MRA in determining the main hemodynamically relevant stenoses within each of the major renal arteries based at the vessel level.

(f) Sensitivity, specificity, and accuracy of OMNISCAN MRA and non-contrast MRA in the combined detection of the main hemodynamically relevant stenoses in each of the 2 major renal arteries.

(g) Description of the COD in determining the most appropriate revascularization strategy based on non-contrast MRA, OMNISCAN MRA, and IA DSA, respectively.

(h) Sensitivity in detecting accessory renal arteries identified by OMNISCAN MRA and non-contrast MRA.

(i) Description of image quality and number of segments evaluable in the renal region for each modality.

Safety:
- Adverse events (AEs) were assessed for occurrence, relationship to OMNISCAN, severity, and seriousness throughout the study up to 72 hours after contrast injection.
- Limited physical examination, vital signs, 12-lead electrocardiograms (ECGs), injection site monitoring, and laboratory parameter assessments were performed at predetermined intervals from baseline to the end of the study.
- The safety of OMNISCAN administration 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 estimated sensitivity and specificity per reader was compared with a selected threshold value of 0.75 (75%) for sensitivity and 0.60 (60%) for specificity.
The null hypotheses:

H_0: P_{0Se}=0.75 versus the alternative hypothesis H_A: $P_{ASe} \neq 0.75$; and
H_0: P_{0Sp}=0.60 versus the alternative hypothesis H_A: $P_{ASp} \neq 0.60$

were tested as co-primary endpoints for each MRA-reader separately using the exact 2-sided binomial test and was based on a significance level of α=0.05. P_0 and P_A are sensitivity and specificity under the null and alternative hypotheses, respectively. In case of a rejection of H_0, an exact 1-sided binomial test based on a significance level of α=0.025 was performed.

The differences in sensitivity and specificity between OMNISCAN MRA and non-contrast MRA 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.

Summary of Results

Efficacy:

- The primary endpoints of sensitivity and specificity for OMNISCAN MRA compared with IA DSA based on the PP population analysis achieved statistical significance in meeting the pre-specified threshold values of 75% for sensitivity and 60% for specificity for the same 2 out of 3 independent blinded MRA readers in both the first and second blinded reads. The co-primary efficacy endpoints of the study were met.
- Analyses performed at the vessel level and using the ITD population were consistent with the primary analysis.
- OMNISCAN MRA was statistically superior to non-contrast MRA in terms of sensitivity and specificity for all 3 independent readers at the subject level for both the PP and ITD population analyses. At the vessel level OMNISCAN MRA was statistically superior in terms of sensitivity in 2 of 3 independent blinded readers for the PP population and in all 3 readers for the ITD population analyses. OMNISCAN MRA was statistically superior for all 3 blinded readers in regard to specificity for both the PP and ITD population analyses.
- In the subset of subjects whose non-contrast MRA was classified as uninterpretable but whose OMNISCAN MRA was classified as interpretable by the blinded readers OMNISCAN MRA demonstrated sensitivity of 80% to 89% with one reader achieving statistical significance at the pre-specified threshold of 75%. All 3 readers achieved statistical significance for specificity at the pre-specified threshold of 60%. In the vessel level analysis 2 readers achieved statistical significance for sensitivity and all 3 readers achieved it for specificity.
- OMNISCAN MRA substantially reduced imaging time and signal loss in renal arteries when compared to non-contrast MRA. Overall image quality and image evaluability for the OMNISCAN MRA images were comparable to those for IA DSA and better when compared to non-contrast MRA.

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Summary of Results (cont'd)

Safety:

- OMNISCAN was well tolerated in subjects with known or suspected RAS.
- Among the 393 subjects who received OMNISCAN, 67 subjects (17%) experienced a total of 83 AEs. Most of the AEs were rated mild in intensity (73%). Four AEs (5%) were rated as severe (injection site hemorrhage, increase of blood CPK, decrease of blood calcium, renal cell carcinoma stage unspecific) but none were considered by the Investigator to be related to OMNISCAN.
- Overall, the most commonly reported AEs were injection site hemorrhage (3%), headache (2%), hematoma (2%), nausea (1%), and diarrhea (1%). All other AEs were reported by <1% of subjects.
- Four subjects (1%) experienced 4 AEs that were considered by the Investigator to be related to OMNISCAN: feeling hot (mild intensity), diarrhea (mild intensity), hot flushes (mild intensity), and pruritus (moderate intensity).
- 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. Only 1 subject had an injection site-related AE that was considered by the Investigator to be severe in intensity.
- Three subjects (<1%) experienced 3 SAEs, none of which were considered by the Investigator to be related to OMNISCAN. Of these, 1 subject had renal failure that resulted in withdrawal from the study and the subsequent death of the subject, 1 subject had a renal cell carcinoma, and 1 subject had an injection site hemorrhage that resulted in prolonged hospitalization. No other AE resulted in death or withdrawal from the study.
- Clinical laboratory parameters (serum chemistry and hematology), vital sign measurements (systolic and diastolic BP, HR, and respiration rate) and ECG measurements (PR, RR, QRS, QT and QTc intervals) generally remained within normal limits following OMNISCAN administration throughout the 24-hour follow-up. Evaluation of pre- and post-administration data indicated that no clinically significant changes were evident following administration of OMNISCAN. No clinically significant trends or safety signals were noted. 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 RAS that compared very favorably with the SOT, IA DSA, used in this study. The primary and secondary analyses lead us to conclude that OMNISCAN MRA was consistently superior to non-contrast MRA. Additional clinical benefits were evident in terms of more rapid image acquisition and better image quality.

The safety assessments performed in this study did not identify any trends or safety concerns related to OMNISCAN administration.

In conclusion, OMNISCAN was safe and efficacious for CE MRA in detection of RAS at the recommended dose of 0.1 mmol/kg.