Clinical Study Report Synopsis **GE Healthcare**
GE-041-075

Title: A post-marketing safety study in patients with moderate renal insufficiency who receive OMNISCAN™ (Gadodiamide Injection) for contrast-enhanced magnetic resonance imaging (MRI)

This is an exact copy of the synopsis from the final clinical study report for the study GE-041-075. The final clinical study report (document-identifier: GE-041-075 CREP) was authorized for use on 27-May-2014 (Version 1.0).

<table>
<tr><td>Name of Sponsor/Company:
GE Healthcare Ltd. and its Affiliates
Name of Finished Product:
Omniscan™
Name of Active Ingredient:
Gadodiamide Injection (Gd-DTPA-BMA)</td><td>Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:

Volume:

Reference:</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="3">Title of Study: A post-marketing safety study in patients with moderate renal insufficiency who receive Omniscan (Gadodiamide Injection) for contrast-enhanced magnetic resonance imaging (MRI)</td></tr>
<tr><td colspan="3">Investigators and Study Centers: 24 centers in 6 countries worldwide (Canada, China, India, Spain, Taiwan, and United States)</td></tr>
<tr><td colspan="2">Study Period: 10 Jun 2009 to 10 Jun 2013</td><td>Phase of Development: Phase 4</td></tr>
<tr><td colspan="3">Objective:
Primary Objective: To capture post-marketing safety information in patients with moderate renal insufficiency (eGFR ≥30 and <60 mL/min/1.73 m^2) undergoing routine contrast-enhanced MRI with administration of Omniscan in order to assess the risk for developing nephrogenic systemic fibrosis (NSF). The index Omniscan administration for each patient was defined as the initial administration of Omniscan per protocol following study entry.
The study was conducted to satisfy a post-marketing requirement from FDA that was withdrawn partway through at which point enrollment was halted.</td></tr>
<tr><td colspan="3">Study Design: The study was designed as an international, multi-center, post-marketing surveillance study in patients with moderate renal insufficiency (estimated glomerular filtration rate [eGFR] ≥30 and <60 mL/min/1.73 m^2) who were administered gadodiamide (Omniscan) for a clinically indicated MRI examination.</td></tr>
<tr><td colspan="3">Selection of Subjects:
Inclusion Criteria:
Subjects were required to fulfill the following criteria in order to be enrolled:
(1) The subject was ≥18 years of age at time of study entry.
(2) The subject was physically able and willing to comply with study procedures and a signed and dated informed consent was obtained.
(3) The subject had been referred for a clinically indicated MRI examination with a gadolinium-based contrast agent (GBCA).
(4) The subject had known or suspected chronic kidney disease with an eGFR ≥30 and <60 mL/min/1.73 m^2 as measured within 30 days prior to the planned index Omniscan administration. GFR was estimated for all subjects using the Modification of Diet in Renal Disease (MDRD) GFR extended version calculator.
(5) The subject agreed to be contacted for follow-up for 24 months.</td></tr>
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Exclusion Criteria:
Subjects with any of the following criteria were not to be enrolled in this study:

(1) Patients with known or suspected NSF based on biopsy confirmation or the onset of signs and symptoms of NSF lasting at least 7 days as follows: (1) skin – swelling, hardening and tightening; reddened or darkened patches; burning or itching ; (2) eyes – yellow raised spots on whites of eyes; or (3) bones and muscle – stiffness in joints; difficulty in moving or straightening of arms, hands, legs or feet; bone pain especially in hips and ribs or muscle weakness.
(2) Patients had known allergies to any GBCA.
(3) Patients had chronic renal disease with a GFR <30 mL/min/1.73 m^2 as measured within 30 days prior to the planned index Omniscan administration.
(4) Patients had acute renal insufficiency of any severity due to the hepato-renal syndrome or were in the peri-operative liver transplantation period.
(5) Patients that were exposed to any GBCA within a period of 12 months prior to the planned index administration of Omniscan.

Number of Subjects (planned and analyzed):
Planned: 600 subjects at up to 100 centers
Enrolled: 213 subjects at 24 centers
Analyzed: 202 subjects at 24 centers

Treatment of Subjects
Investigational Medicinal Product: The volume and injection rate of Omniscan administered intravenously were at the discretion of the investigator/designee based upon routine MRI practices and following the product package insert prescribing information (PI).
Duration of Treatment: Contrast media was administered for the MRI procedure only, followed by a 24 hour AE follow-up visit.
Late Follow-up Duration: Subjects were further evaluated for NSF symptoms at 1, 3, 6, 12, 18 and 24 month visits.

Endpoints
Efficacy: There were no efficacy endpoints in this study.
Safety: The primary endpoint analysis was the incidence of NSF, based on clinical signs and symptoms, with or without biopsy confirmation. The secondary endpoint was the incidence of NSF that was confirmed histologically (biopsy confirmation).

Statistical Analyses
All enrolled subjects who received any dose of Omniscan were included for analyses. Displays of summarized demographic data included age, gender, race, and weight. Medical and surgical history data recorded at screening were listed by subject. Prior and concomitant medications were summarized for safety analyses. In addition, the number and percentage of subjects who discontinued from the study were summarized by reason for each treatment group and overall.

Safety Analysis:
The primary safety analysis consisted of:

- The incidence of NSF based on clinical signs and symptoms with or without biopsy confirmation was estimated for the study population with 95% exact confidence intervals e.g., Clopper-Pearson.

The secondary safety analysis consisted of:

- The incidence of NSF based on biopsy confirmation was estimated for the study population with 95% exact confidence intervals e.g., Clopper-Pearson.

Other Safety Analysis:
The number and percentage of female pregnancies were to be summarized as specified in the original study protocol. None of the subjects met these criteria.

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<tr><td colspan="3">Adverse Events:
Serious Adverse Events (SAEs) reported on the case report forms (CRFs) were mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA, version 16.0) coding dictionary. The following listings were produced by treatment and subject:
o All SAEs.
o Treatment-emergent SAEs (TEAEs) were flagged and summarized
o All Serious Adverse Drug Reactions (SADRs) were flagged.
The number and percentage of subjects experiencing SAEs were summarized for the following AE categories:
o Any SAE
o Any SAE by intensity
o Any SAE by outcome
o Any SAE determined to be a SADR
o Any SAE leading to death</td></tr>
<tr><td colspan="3">Summary of Results
<u>Efficacy:</u> Not applicable to this study.
<u>Safety:</u>
• The incidence of NSF based on clinical signs and symptoms with or without biopsy confirmation was estimated for the study population with 95% CI. Upon further clinical evaluation none of the subjects were diagnosed with NSF.
• Seven subjects reported 12 serious TEAEs during the study of which only 1 event (azotemia) was considered related to Omniscan. The most commonly affected organ system for SAEs was skin and subcutaneous tissue disorders.</td></tr>
<tr><td colspan="3">Conclusions: The number of reported NSF cases has declined dramatically since 2007 with the implementation of improved screening of patients for renal insufficiency. In this study, we did not identify any NSF cases in patients with moderate renal insufficiency (eGRF ≥30 and <60 ml/min/1.73 m^2). The results of this study support the safe labeled use of Omniscan in patients with appropriate renal function.</td></tr>
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