Clinical Study Report Synopsis **GE Healthcare**
GE-012-097

Title: A Phase 4, Randomized, Double-blind Study Comparing Patient Comfort and Safety between Iodixanol 320 mg I/mL and Iopamidol 370 mg I/mL in Patients Undergoing Contrast-Enhanced Computed Tomographic Imaging of the Abdomen/Pelvis

This is an exact copy of the synopsis from the final clinical study report for the study GE-012-097. The final clinical study report (document-identifier: GE-012-097 CREP) was authorized for use on 18-Jun-2012 (Version 1.0).

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Title of Study: A Phase 4 Randomized, Double-blind Study Comparing Patient Comfort and Safety between Iodixanol 320 mg I/mL and Iopamidol 370 mg I/mL in Patients Undergoing Contrast-Enhanced Computed Tomographic (CECT) Imaging of the Abdomen/Pelvis		
Investigators and Study Centers: Nine centers in the United States and Europe.		
Investigators and Centers for Independent Evaluation of Images: CECT image quality was assessed by an on-site radiologist/investigator (blinded to the contrast administered) at each study center.		
Publication (reference): None		
Study Period: 03 Jun 2011 to 27 Oct 2011	**Phase of Development:** Phase 4	

Objectives:

Primary:

- To evaluate and compare overall patient comfort profile between the Iso-osmolar contrast media (IOCM), iodixanol 320 mg I/mL, and a Low-osmolar contrast media (LOCM), iopamidol 370 mg I/mL in patients undergoing CECT imaging of the abdomen/pelvis.
  The patient discomfort is defined as a sensation of coldness, heat or pain experienced by the patient that is temporally associated with the injection/infusion of a contrast medium (CM).

Secondary:

- To evaluate and compare the impact of patient discomfort on image procedure and overall image quality.
- To evaluate and compare the overall safety profile in terms of occurrence of adverse events (AEs).

Study Design:

This study was designed as a prospective, multi-center, double-blind, randomized, parallel group comparative study of iodixanol (320 mg I/mL) and iopamidol (370 mg I/mL) in patients undergoing CECT imaging of the abdomen/pelvis as part of their routine medical care.

All subjects were randomized in a 1:1 ratio to receive iodixanol (320 mg I/mL) or (iopamidol 370 mg I/mL) as the CM for the exam. The CM was administered as an undiluted intravenous bolus injection via power injector. The presence or absence of patient discomfort in terms of sensations of coldness, heat and pain associated with the CM administration was assessed immediately following the computed tomography (CT) scan and recorded. The intensity of pain and sensations of coldness and/or heat were rated verbally by the patient on a scale of 0 to 10.

The impact of patient discomfort on the CT procedure was recorded as: whether the scan was repeated (either

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with CT or another imaging modality) due to subject motion and, if so, the modality, date and time of the re-scan, the detailed reason for the re-scan, the type and volume of any additional contrast used, radiation dose, and imaging center time required to complete the re-scan were recorded.
Other safety assessments included follow-up for AEs up to 24 hours post contrast administration.

Selection of Subjects:
Inclusion Criteria:
Subjects were included in the study if they met all of the following criteria:
(1) The subject was over 18 years old.
(2) Subjects were referred to undergo a CECT imaging of the abdomen/pelvis as part of their routine clinical care.
(3) The subject had provided signed and dated informed consent.
Exclusion criteria:
Subjects were excluded from participating in this study if they met the following criteria:
(1) The subject had known allergies to iodine or any prior history of adverse reaction to iodinated CM.
(2) The subject had received another administration of CM within 24 hours prior to baseline or was scheduled to receive one within the 24 hour follow-up period.
(3) The subject was pregnant.
(4) The subject was taking metformin (e.g., Glucophage®) but was not willing or unable to discontinue at the time of the study procedure.
Note: Metformin could not be taken at least 24 hours prior to the study procedures; had to be withheld for at least 48 hours post-procedure, and could be restarted only after the subjects renal function had been evaluated and it was deemed safe to resume metformin.
(5) The subject manifested thyrotoxicosis or was on dialysis.
(6) The subject was previously included in this study.
(7) The subject had an unstable clinical condition where study participation may have compromised the management of the subject or other reason that in the judgment of the investigator made the subject unsuitable for participation in the study.

Number of Subjects (planned and analyzed):
Planned: Approximately 300 subjects at up to 20 centers.
Enrolled: 304 subjects at 9 centers.
Analyzed: 299 subjects at 9 centers.

Treatment of Subjects
Investigational Medicinal Product: Iodixanol 320 mg I/mL (VISIPAQUE™) was administered intravenously at the discretion of the prescribing physician based upon institutional requirements for the CECT procedures. The product package insert was consulted for the prescribing information.
Comparator: Iopamidol 370 mg I/mL was the comparator in the study and was injected intravenously at the discretion of the prescribing physician based upon institutional requirements for the CECT procedures. The product package insert was consulted for the prescribing information.
Duration of Treatment: CM was administered for the CECT procedure only, followed by a 24 hour AE follow-up period.

Endpoints
Efficacy:
The primary efficacy endpoint for the study was the categorical classification of image quality based on the presence or absence of motion artifacts. The CECT image quality was assessed by an on-site radiologist/investigator (who was also blinded to the contrast administered) at the study center.
The overall image quality was graded on a three-point scale based only on the presence or absence of motion artifacts:

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- excellent (no motion),
- adequate (mild motion but resulting in a diagnostic image) or
- poor (severe motion which either significantly degrades diagnostic confidence or results in a recommendation to acquire a repeat scan using either CECT or another imaging modality).

The secondary efficacy endpoints for the study were the number of subjects in whom the scan needed to be repeated based on the poor quality of the initial scan, and the impact of patient discomfort on image procedure. If the scan was repeated using CECT, the same clinician reviewed and graded both images using the above criteria.

Safety:

The primary safety endpoint was the comparison of the maximum intensity of patient discomfort between iodixanol 320 mg I/mL and iopamidol 370 mg I/mL as rated by the subjects within 10 minutes of intravenous contrast administration for their CECT imaging of the abdomen/pelvis.

Patient discomfort included sensations of coldness, heat or pain. The subject was asked to separately rate the maximum intensity of the sensations of pain, warmth and coldness on a scale of 0-10 following the main bolus injection of CM and completion of the CT scan.

The maximum intensity of patient discomfort score for each type was converted into 4 categories: none = 0; mild= 1-3, moderate = 4-7; severe = 8-10. The overall patient discomfort was defined as the maximum intensity of any individual discomfort score (i.e., pain, warmth or coldness).

The secondary safety endpoints were

- Frequency of subject experiencing discomfort following intravenous administration of either iodixanol 320 mg I/mL or iopamidol 370 mg I/mL for CECT scan.
- Maximum intensity and frequency of the coldness, heat, and pain reported by subjects following administration of iodixanol 320 mg I/mL or iopamidol 370 mg I/mL.
- Incidence rates of the overall AEs and SAEs within 24 hours following administration of either iodixanol 320 mg I/mL or iopamidol 370 mg I/mL.
- Relationship between patient discomfort (pain, coldness or heat) and common risk factors, including but not limited to, age, gender, location of injection, injection rate, contrast type and volume, use of a contrast warmer, and needle/catheter size, prior history of contrast administration, peripheral vascular disease or connective tissue disease (e.g., Raynaud phenomenon or other vasculitis).

Statistical Analyses:

Demographic variables and other baseline characteristics were summarized descriptively by treatment assignment and overall, independent of investigational medicinal product (IMP) assignment. Demographic variables included age, weight, height, gender, and race/ethnicity.

Efficacy Analyses:

The primary efficacy analyses consisted of:

- The CECT image quality was compared between the randomized treatment groups using a generalized linear model specifying the distribution of the dependent variable as multinomial. The proportion of scans that needed to be repeated was also compared using a generalized linear model specifying the distribution of the dependent variable as binomial.
- The distributions of the categorical classification of the image quality in the iodixanol 320 mg I/mL and iopamidol 370 mg I/mL groups were compared using a generalized linear model specifying the distribution of the dependent variable as multinomial.

The secondary efficacy analyses consisted of:

- The proportion of scans that were repeated in the treatment groups was compared using a logistic regression model. The dependent variable in the model was the presence of a repeated scan.
- The proportion of subjects whose discomfort following intravenous administration of iodixanol 320 mg

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I/mL and iopamidol 370 mg I/mL impacted the CECT procedure was compared in the 2 groups using a logistic regression model. The dependent variable in the model was the presence or absence of the subject's discomfort impacting the CECT procedure (yes or no).

Safety Analyses:

The primary safety analysis consisted of:

- The distribution of subjects with moderate/severe discomfort was compared in the iodixanol 320 mg I/mL and iopamidol 370 mg I/mL groups using a logistic regression model. The dependent variable in the model was presence or absence of moderate/severe discomfort (yes or no).

The secondary safety analyses consisted of:

- The proportion of subjects experiencing any discomfort following intravenous administration of iodixanol 320 mg I/mL and iopamidol 370 mg I/mL for CECT scan was compared in the 2 groups using a logistic regression model. The dependent variable in the model was presence or absence of any discomfort.
- The maximum intensity of patient discomfort following intravenous administration of iodixanol 320 mg I/mL and iopamidol 370 mg I/mL was compared in the 2 groups using the pooled results from all 3 sub-scales (coldness, heat or pain). The distribution of subjects with none, mild, moderate, and severe discomfort was compared using a generalized linear model specifying the distribution of the dependent variable as multinomial. The dependent variable in the model was the distribution of discomfort scores.
- Patient discomfort following intravenous administration of iodixanol 320 mg I/mL and iopamidol 370 mg I/mL was compared in the 2 groups separately for each of the 3 sub scales (coldness, heat, or pain). The distribution of subjects with none, mild, moderate, and severe discomfort was compared using a generalized linear model specifying the distribution of the dependent variable as multinomial. The dependent variable in the model was the distribution of discomfort scores.
- The proportion of subjects experiencing discomfort following intravenous administration of iodixanol 320 mg I/mL and iopamidol 370 mg I for CECT scan was compared in the 2 groups separately for each of the 3 sub-scales (coldness, heat, or pain) by using a logistic regression model. The dependent variable in the model was the presence or absence of any discomfort for each sub-scale.
- The sum of the patient discomfort scores following intravenous administration of iodixanol 320 mg I/mL and iopamidol 370 mg I/mL was compared in the 2 groups using the pooled results from all 3 sub-scales (coldness, heat or pain). The sum of the patient discomfort scores was compared in the 2 groups using a linear regression model. The dependent variable in the model was the sum of the discomfort score.

Additional safety analysis consisted of:

- The distribution of subjects with severe discomfort was compared in the iodixanol 320 mg I/mL and iopamidol 370 mg I/mL groups using a logistic regression model. Additional analyses of the distribution of subjects were conducted separately for subjects with severe pain, subjects with severe heat, and subjects with severe cold. For each of these 4 analyses, the dependent variable in the model was the presence or absence of severe discomfort, severe pain, severe heat, or severe cold.

Adverse Events:

Treatment-emergent AEs (TEAEs) reported on the case report forms (CRFs) were mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA, version 14.0) coding dictionary. The number and percentage of patients reporting each event were summarized during the treatment phase by treatment assignment.

TEAEs were summarized as follows:

- Overall number (frequency) of TEAEs.
- TEAEs by maximum severity, relationship to study drug, seriousness, and outcome
- TEAEs causing discontinuation from the study.

Analysis Populations:

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Three analysis populations were defined and analyzed for this study: the efficacy population (full analysis set [FAS]), the per-protocol (PP) population, and the safety population (safety analysis set [SAS]).

- The FAS included 299 enrolled subjects (151 iodixanol, 148 iopamidol) who were administered one of the study drugs, and had images that were technically evaluable for image quality assessment.
- The PP population included 222 enrolled subjects (114 iodixanol, 108 iopamidol) who were administered one of the study drugs, had images that were technically evaluable for image quality assessment, had an evaluable discomfort score within 10 minutes of intravenous contrast administration for their CECT imaging of the abdomen/pelvis, and had no major protocol violations.
- The SAS consisted of 299 subjects (151 iodixanol, 148 iopamidol) who were enrolled in the study (signed informed consent) and who received one of the study drugs.

Summary of Results

Efficacy:

- The proportion of subjects with excellent overall image quality was greater for the iodixanol 320 mg I/mL group (144/151 [95.4%] subjects) compared to the iopamidol 370 mg I/mL group (133/148 [89.9%] subjects), for the FAS. Similar results were obtained for the PP population analysis.
- There was a statistical trend for the distributions of overall image quality to differ between the iodixanol group and iopamidol groups (p=0.0508), for the FAS. For the PP population, the distributions of overall image quality were statistically significantly different between the iodixanol and iopamidol treatment groups (p=0.0401).
- • The distributions of overall image quality were statistically significantly different between the US and EU geographical regions (p<0.0001). Similar results were obtained for the PP population analysis.
- No subjects required a repeated CECT scan due to poor image quality of the initial scan.
- The impact of patient discomfort on overall quality of the image was not statistically significantly different between the treatment groups (p=0.9953), for the FAS. Discomfort impacted the overall quality of the image for 9/151 (6.1%) iodixanol subjects and 9/148 (6.0%) iopamidol subjects. Similar results were obtained for the PP population analysis.

Safety:

- The proportion of patients that experienced moderate/severe discomfort was statistically significantly lower for the iodixanol group (53/151 [35.1%] subjects) compared to the iopamidol group (99/147 [67.3%] subjects) (p<0.001), for the SAS. Similar results were obtained for the PP population analysis.
- The proportion of subjects that experienced moderate/severe heat was statistically significantly lower for the iodixanol group (45/151 [29.8%] subjects) compared to the iopamidol group (94/147 [63.9%] subjects) (p<0.0001), for the SAS. Similar results were obtained for the PP population analysis.
- The proportion of subjects that experienced severe discomfort was statistically significantly lower for the iodixanol group (4/151 [2.6%] subjects) compared to the iopamidol group (24/147 [16.3%] subjects) (p=0.0004), for the SAS. Similar results were obtained for the PP population analysis.
- The proportion of subjects that experienced severe heat was statistically significantly lower for the iodixanol group (4/151 [2.6%] subjects) compared to the iopamidol group (22/147 [15.0%] subjects) (p=0.0008), for the SAS. Similar results were obtained for the PP population analysis.
- The proportion of subjects without any discomfort was statistically significantly higher for the iodixanol group (32/151 [21.2%] subjects) compared to the iopamidol group (11/147 [7.5%] subjects) (p=0.0008). Similar results were obtained for the PP population analysis. Overall, the proportion of subjects with any discomfort was statistically significantly lower for the iodixanol group (119/151 [78.8%] subjects) compared to the iopamidol group (136/147 [92.5%] subjects) (p=0.0012), for the SAS. In addition, the proportion of subjects with heat discomfort was statistically significantly lower for the iodixanol group (108/151 [71.5%] subjects) compared to the iopamidol group (128/147 [87.1%] subjects) (p=0.0012).

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Similar results were obtained for the PP population analyses.

- The distributions of maximum patient discomfort scores were statistically significantly different between the treatment groups ($p<0.0001$), for the SAS. For the heat discomfort category, the distributions of maximum patient discomfort scores were statistically significantly different between the treatment groups ($p<0.0001$). Similar results were obtained for the PP population analyses.
- The mean (SD) sum of patient discomfort scores was statistically significantly lower for the iodixanol group (3.1 [2.57]) compared to the iopamidol group (5.1 [3.24]) ($p<0.0001$), for the SAS. Similar results were obtained for the PP population analysis.
- There were no AEs leading to death or study discontinuation reported during the study. There was one SAE reported for a subject in the iopamidol group, acute appendicitis of moderate intensity and unrelated to treatment.
- The proportion of subjects experiencing any AE was statistically significantly lower for the iodixanol group (121/151 [80.1%] subjects) compared to the iopamidol group (134/148 [90.5%] subjects) ($p=0.0139$).
- The proportion of subjects with an AE that was considered related to contrast administration was statistically significantly lower for the iodixanol group (120/151 [79.5%] subjects) compared to the iopamidol group (134/148 [90.5%] subjects) ($p=0.0093$).
- The proportions of subjects with moderate and severe intensity AEs were statistically significantly lower for the iodixanol group compared to the iopamidol group ($p=0.0146$ and $p=0.0058$, respectively).
- The proportion of subjects with General disorders and administration site conditions AEs was statistically significantly lower for the iodixanol group (117/151 [77.5%] subjects) compared to the iopamidol group (133/148 [89.9%] subjects) ($p=0.0047$). Within this system organ class, the proportions of subjects with Feeling hot and Injection site reaction AEs were lower for the iodixanol group compared to the iopamidol group. The majority of AEs were of mild intensity and all were considered related to treatment.
- The proportion of subjects with Skin and subcutaneous skin disorders was statistically significantly greater for the iodixanol group (7/151 [4.6%] subjects) compared to the iopamidol group (0/148 [0.0%] subjects) ($p=0.0146$). For two iodixanol subjects (2/151 [1.3%]), urticaria AEs of moderate intensity were considered related to treatment. Literature and the adverse drug reaction reports show that these skin reactions from iodixanol administration are generally mild, are of short duration, and resolve spontaneously.

Conclusions:

Iso-osmolar iodixanol 320 mg I/mL use resulted in less frequent and severe patient discomfort than the use of low-osmolar iopamidol 370 mg I/mL in patients undergoing CECT imaging of the abdomen/pelvis as part of their routine medical care. A greater proportion of subjects in the iodixanol group had excellent overall image quality. Iodixanol use resulted in a lower frequency of AEs over 24 hours after administration of CM.