Clinical Study Report Synopsis **GE Healthcare**
GE-012-098

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 Peripheral Arteriography

This is an exact copy of the synopsis from the final clinical study report for the study GE-012-098. The final clinical study report (document-identifier: GE-012-098 CREP) was authorized for use on 16-Dec-2013 (Version 1.0).

<table>
<tr><td>Name of Sponsor/Company:
GE Healthcare Ltd. and its Affiliates
Name of Finished Product:
VISIPAQUE™
Name of Active Ingredient:
Iodixanol</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 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 Peripheral Arteriography</td></tr>
<tr><td colspan="3">Investigators and Study Centers: Thirteen centers in the US and Europe participated in the study.</td></tr>
<tr><td colspan="3">Investigators and Centers for Independent Evaluation of Images: Angiographic image quality was assessed by the Investigator or an on-site radiologist (blinded to the contrast administered) at each study center.</td></tr>
<tr><td colspan="3">Publication (reference):None</td></tr>
<tr><td colspan="2">Study Period: 01 Nov 2011 to 06 Feb 2013</td><td>Phase of Development: Phase 4</td></tr>
<tr><td colspan="3">Objectives:
Primary:
To evaluate and compare overall patient comfort profile between an iso-osmolar contrast medium (IOCM), iodixanol 320 mg I/mL, and a low osmolar contrast medium (LOCM), iopamidol 370 mg I/mL, in patients undergoing peripheral arteriography examinations.
In this study, the patient discomfort is defined as a sensation of coldness, heat and injection-associated pain experienced by the patient that was temporally associated with the injection/infusion of a contrast medium.
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 within 24 hours following the contrast media (CM) administration.</td></tr>
<tr><td colspan="3">Study Design:
This was a prospective, multi-center, randomized double-blind, parallel group comparative study of VISIPAQUE™ (iodixanol) Injection 320 mg I/mL (referred to as iodixanol 320 hereafter) and ISOVUE®-370 (iopamidol Injection 76%) (referred to as iopamidol 370 hereafter) in patients undergoing peripheral arteriography examinations as part of their routine medical care. The peripheral arteriography in this study included upper or lower extremity or carotid arteriograms.
The peripheral arteriography was performed at each site following their routine procedural protocol. All subjects were randomized to receive either the IOCM, iodixanol 320, or the LOCM comparator, iopamidol 370. The CM volume and injection rate were determined by patient needs and the parameters of the specific</td></tr>
</table>

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates **Name of Finished Product:** VISIPAQUE™ **Name of Active Ingredient:** Iodixanol	**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)**

arteriographic procedure performed.

The presence or absence of contrast-induced discomfort in terms of sensation of coldness or heat and injection-associated pain were assessed immediately (≤10 minutes) following each contrast administration 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.

Since each subject had multiple contrast injections during the angiography procedure, the contrast-induced discomfort information was collected after each contrast administration by procedural phase (diagnostic or intervention) and compiled as maximum patient discomfort across overall contrast injections, which was consisted of discomfort from first (initial) injection and the rest injections (excluding the initial injection).

The impact of patient discomfort on image procedure was recorded as to whether the procedure was repeated due to either subject motion or insufficient contrast (causing poor image acquisition) and, if so, the location of the image re-taken, the reason, the type and volume of any additional contrast used, radiation dose, and imaging centre time required to complete the re-take were recorded. If no repeated acquisition was performed for the poor images, the reason was recorded.

Other safety assessments included follow-up adverse events (AEs) 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) The subject was referred to undergo a peripheral arteriography 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 any of the following criteria:

(1) The subject had known allergies to iodine or any prior history of adverse reaction to iodinated CM.

(2) The subject received another administration of CM within 24 hours prior to baseline or was scheduled to receive one within 24 hours after completion of the arteriography procedure (i.e., follow-up period).

(3) The subject was pregnant or lactating.

(4) The subject was taking metformin (e.g., Glucophage®) but was not willing or was unable to discontinue at the time of the study procedure.

Note: Metformin could not be taken for at least 24 hours prior to the study procedures, had to be withheld for at least 48 hours post-procedure, and restarted only after the subject's renal function had been evaluated and it was deemed safe to resume metformin.

(5) The subject manifested thyrotoxicosis or is on dialysis.

(6) The subject was previously included in this study.

(7) The subject had 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.

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates **Name of Finished Product:** VISIPAQUE™ **Name of Active Ingredient:** Iodixanol	**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)**

Number of Subjects (planned and analyzed):
Planned: 250 subjects at 15 centers
Enrolled: 255 subjects at 13 centers
Analyzed: 253 subjects at 13 centers

Treatment of Subjects:

Investigational Medicinal Product: VISIPAQUE™ (iodixanol) Injection 320 mg I/mL was used as a test agent for the peripheral arteriography. It was administered intra-arterially at the discretion of the prescribing physician based upon the imaging center's routine practices for peripheral arteriography and following the package insert (PI) or Summary of Product Characteristics (SPC) instructions.

Comparator: ISOVUE®-370 (Iopamidol Injection 76%) was the comparator in this study and was injected intra-arterially. The volume and injection rate were at the discretion of the prescribing physician based upon the imaging center's routine practices for the peripheral arteriography and following the PI or SPC instructions.

Duration of Treatment: CM was administered for the peripheral arteriography procedure only, followed by a 24 hour AE follow-up period.

Endpoints:

Primary Endpoint:

Comparison of the maximum intensity composite score of patient discomfort between iodixanol 320 and iopamidol 370 as rated by the subjects within 10 minutes of intra-arterial contrast administration for their peripheral arteriography.

Patient discomfort included sensations of coldness, heat or pain. Following each CM injection, the subject was asked to separately rate the sensations of coldness, warmth or pain on a scale of 0-10. The overall patient discomfort was defined as the maximum patient discomfort of any of the 3 categories (i.e., pain, warmth or coldness).

The intensity of patient discomfort (i.e., pain, heat or coldness) score was then classified as one of the following categories:

- none = 0
- Mild= 1-3
- Moderate = 4-7
- Severe = 8-10

Secondary Endpoints:

- Frequency and severity of subject motion impacting diagnostic quality of the images between iodixanol 320 and iopamidol 370.
- Frequency of patient discomfort reported by the subject following intra-arterial administration of either iodixanol 320 or iopamidol 370 for peripheral arteriography.
- Frequency of subjects with either coldness or heat or injection-associated pain following administration of iodixanol 320 or iopamidol 370.
- Maximum intensity of the coldness or heat or injection-associated pain following the first or overall administration of iodixanol 320 or iopamidol 370.
- Incidence rates of the overall AEs and SAEs in 24 hours following administration of either iodixanol 320 or iopamidol 370.
- Correlating patient discomfort (coldness or heat and injection-associated pain) with 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, patient sedation status, prior history of contrast

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates	**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: VISIPAQUE™		
Name of Active Ingredient: Iodixanol	**Volume:**	
	Reference:	

administration, peripheral vascular disease or connective tissue disease (e.g., Raynaud phenomenon or other vasculitis).

Statistical Analyses

All randomized subjects who received any study drug were included for the overall safety, i.e., treatment-emergent adverse event (TEAE) analyses. The primary population for subject comfort analysis consisted of all randomized subjects who received any study drug administration and complete post-injection evaluation. Demographic variables and subject characteristics were summarized descriptively by treatment assignment and overall, independent of IMP assignment. Demographic variables included age, weight, height, gender, and race/ethnicity.

Primary Analysis

Subject discomfort within 10 minutes of intra-arterial contrast administration was determined using a categorical scale. Overall subject discomfort was defined as the maximum of the 3 individual discomfort rating scales: intense pain, hot, and cold. The maximum intensity of subject discomfort was converted into 4 categories: none = 0; mild= 1-3, Moderate = 4-7; severe = 8-10. The primary method of analysis was based on a comparison of proportions between the 2 randomized treatment groups. The proportions of subjects with a discomfort classification of moderate or severe (4-10) were compared between subjects who received iodixanol 320 to those who received iopamidol 370 during the peripheral arteriography. Probability values < 0.05 were considered significant.

Since there were multiple contrast injections during each procedure and contrast-induced discomfort information was collected after each contrast administration, the convention of data analysis was based on the procedure phase and injection stage.

The procedure phase included diagnostic phase for every subject and interventional phase for those subjects with subsequent intervention.

In each phase, patient discomfort data were categorized as three stages: all CM injections, initial injection composite score excluding initial injection. All CM injections were defined as maximum patient discomfort across all contrast injections during that phase and divided into initial (first) injection and rest injections (referred as the composite score excluding initial injection) stages. The initial injection represented maximum discomfort from the first contrast injection during that phase; and the composite score excluding initial injection was the maximum discomfort from rest contrast injections except for the first injection during that phase.

Secondary Analyses

Efficacy:

- The angiographic 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 angiograms that needed to be repeated was also compared using a generalized linear model specifying the distribution of the dependent variable as binomial.

Safety:

- The frequency of subjects with any discomfort following intra-arterial administration of either iodixanol 320 or iopamidol 370 for peripheral arteriography was compared using a generalized linear model specifying the distribution of the dependent variable as binomial.
- The frequency of subjects who reported any discomfort associated with pain, coldness or heat following administration of iodixanol 320 or iopamidol 370 was compared using a generalized linear model specifying the distribution of the dependent variable as binomial.
- Maximum intensity of the coldness or heat or injection-associated pain following the first or overall administration of iodixanol 320 or iopamidol 370 were compared using a generalized linear model

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates	**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: VISIPAQUE™		
Name of Active Ingredient: Iodixanol	**Volume:**	
	Reference:	

specifying the distribution of the dependent variable as multinomial.

- The intra-subject discomfort scores for coldness, heat, and pain were correlated with common risk factors to determine the association.
- TEAEs reported on the case report forms (CRFs) were mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percentage of subjects reporting each event were summarized during the treatment phase by contrast assignment. TEAEs were summarized in the following ways:
  - Overall TEAEs (from randomization until 24 hours after the administration of the contrast agent).
  - TEAEs by maximum severity, relationship to study drug, seriousness, and outcome (from randomization until 24 hours after the administration of the contrast agent).
  - TEAEs causing discontinuation from the study.

Sample Size

The maximum sample size for this clinical investigation was 250 patients, assigned using a balanced design to receive one of the 2 study drugs. The 250 maximum was predicated on to ensure that the study was not underpowered. After 150 patients had been enrolled, an Independent Data Monitoring Committee (IDMC) conducted an interim assessment to determine if a sample size adjustment was required using a Conditional Power approach. The conditional power in the evaluation of frequency of patients with moderate /severe discomfort exceeded 80%.The null hypothesis of the primary endpoint is rejected based on the O'Brien-Fleming (1977) boundary, indicating early success on the one-sided alternative hypothesis on the primary endpoint. If elected, the study may be discontinued at this point in the interim analysis. However, the IDMC was comfortable having the study proceed to its original planned enrolment target. Continued enrolment would add credibility to the study and allow greater power for evaluation of the secondary endpoints

Summary of Results:

Efficacy:

- The proportion of subjects with excellent overall image quality was numerically greater for the iodixanol group (86.5%) compared with the iopamidol group (82.4%) but the difference was not statistically significant (p=0.5731).
- No repeat arteriogram was performed for poor image quality in either contrast group.
- Discomfort impacted the overall quality of the image in a very small percentage of subjects (3.2% in iodixanol group and 6.5% in iopamidol group) in both contrast groups.

Safety:

- The primary safety analysis of contrast-induced patient discomfort showed that the proportion of subjects with moderate/severe maximum discomfort was statistically significantly lower in the iodixanol group compared with the iopamidol group for all CM injections (67.7% vs. 84%, p=0.0028), the initial injection (42.7% vs. 73.6%, p<0.0001), and for the composite score excluding the initial injection (61.7% vs. 78%, p =0.0030) during the diagnostic phase with less moderate/severe pain as primary factors.
- The proportion of subjects with moderate/severe pain during the diagnostic phase was 7.3% in the iodixanol group and 44% in the iopamidol group for all CM injections, 4% vs. 16.8% for the initial injection, and 6.7% vs. 39.8% for the composite score excluding the initial injection. The differences between the two contrast groups were statistically significant for all injection stages (p< 0.0001, p=0.0023, and p<0.0001, respectively).
- The proportion of subjects experiencing severe discomfort in the diagnostic phase was statistically significantly lower in the iodixanol group compared to the iopamidol group for all CM injections (16.9% vs. 46.4%, p<0.0001) and for the composite score excluding the initial injection (15% vs. 42.3%, p <0.0001) but not for the initial injection (9.7% vs. 16.8%, p=0.1024). Similarly, the proportion of subjects

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates	**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: VISIPAQUE™		
Name of Active Ingredient: Iodixanol	**Volume:**	
	Reference:	

experiencing severe pain or heat was statistically significantly lower for the iodixanol group compared to the iopamidol group for all CM injections and the composite score but not for the initial injection.

- For the intervention phase, differences were generally in favor of iodixanol administration and statistically significant for moderate/severe discomfort, heat or pain as well as severe discomfort, heat or pain at various but not all injection stages because less than one-third subjects in the study underwent an intervention.
- In the analysis of patient discomfort scores, a statistically significant lower score for the iodixanol group compared to the iopamidol group was recorded for the initial injection (2.8 vs. 5.1, $p<0.0001$) and the composite score (3.4 vs. 7.1, $p<0.0001$) during the diagnostic phase. The scores during the intervention phase were also lower for iodixanol group with a statistically significant difference for the composite score (2.0 vs. 4.5, $p=0.0015$) but was not significantly different for the initial injection stage (1.5 vs. 2.9, $p=0.0685$).
- Logistical regression analysis demonstrated that contrast administration was a significant independent risk factor for moderate/severe patient discomfort with iodixanol contributing less moderate/severe patient discomfort compared to iopamidol injection during the diagnostic phase for all injection stages ($p<0.0005$, $p<0.0001$, and $p=0.0023$, respectively). Similar results were observed for moderate/severe pain for all injection stages ($p<0.0001$, $p=0.0017$, and $p<0.0001$) and for heat at the all CM injections ($p=0.0153$) and initial injection ($p<0.0001$) but not in the composite score but not for the initial injection ($p=0.0763$).
- In addition to contrast administration, male gender and use of sedative medication were also identified as independent factors to less moderate/severe patient discomfort in all injection stages during the diagnostic phase. The presence of diabetes mellitus (DM) contributed less moderate/severe discomfort for the all CM injection and the initial injection stages but not for the composite score excluding the initial injection ($p=0.2102$).
- A high incidence of TEAEs was reported in both contrast groups during the study due to inclusion of contrast-induced patient discomfort.
- When excluding contrast-induced patient discomfort from the overall TEAEs, there was a slightly higher incidence of TEAEs in the Iodixanol group (18.9%) compared to the iopamidol group (11.9%); but this difference was not statistically significant ($p=0.1632$).
- When excluding contrast-induced patient discomfort from the overall TEAEs, the most frequent TEAEs after iodixanol administration were dizziness (6.3%), followed by photopsia (5.5% subjects). No difference of TEAE incidence was observed in any preferred term between the two contrast groups.
- A total of 4 SAEs occurred during the study, 2 in each contrast group. None of the SAEs was considered related to CM. One subject died in the iopamidol 370 group due to hypovolemic shock.
- One TEAE (heat and pain) led to discontinuation of CM injection in the iopamidol group.

Conclusions: Iodixanol injection induced significantly less moderate/severe patient discomfort, heat or pain and significantly less severe discomfort, heat or pain than did iopamidol. The results of this comparative study support the concept that the higher osmolality of iopamidol is a key contributing factor for patient discomfort, pain or heat and suggest that iodixanol is a preferable contrast agent for use in peripheral arteriography.