Clinical Study Report Synopsis **GE Healthcare**
DXV405

Title: A Multicentre, Randomised, Double-blind, Parallel-group, Phase IV Study to Compare the Effects of the Non-ionic Iso-osmolar Contrast Medium Iodixanol 320 gI/mL (VISIPAQUE™) with the Non-ionic Low-osmolar Contrast Medium Iopamidol 370 mgI/mL in Subjects with Impaired Renal Function and Diabetes Mellitus Undergoing Coronary Angiography with or without Percutaneous Coronary Intervention (PCI)

This is an exact copy of the synopsis from the final clinical study report for the study DXV405. The final clinical study report (document-identifier: DXV405 CREP) was authorized for use on 13-Nov-2009 (Version 1.0).

<table>
<tr><td>Name of Sponsor/Company:
GE Healthcare Ltd. and its Affiliates</td><td rowspan="3">Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:

Volume:

Reference:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
VISIPAQUE™</td></tr>
<tr><td>Name of Active Ingredient:
Iodixanol</td></tr>
<tr><td colspan="3">Title of Study: A multicentre, randomised, double-blind, parallel-group, phase IV study to compare the renal effects of the non-ionic iso-osmolar contrast medium iodixanol 320 mgI/ml (VISIPAQUE™) with the non-ionic low-osmolar contrast medium iopamidol 370 mgI/ml in subjects with impaired renal function and diabetes mellitus undergoing coronary angiography with or without percutaneous coronary intervention (PCI)</td></tr>
<tr><td colspan="3">EudraCT Number: 2004-005002-68</td></tr>
<tr><td colspan="3">Investigators and Study Centre(s): Sixty-three centres in Europe, India, and North America.</td></tr>
<tr><td colspan="3">Publication (reference): Laskey W, et al. Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures. AHJ, in press.</td></tr>
<tr><td colspan="2">Study Period: 25 August 2005 to 26 February 2007</td><td>Phase of Development: 4</td></tr>
<tr><td colspan="3">Objectives:
Primary:
• To evaluate and compare the effects of 2 different contrast media (CM), iodixanol 320 mgI/ml and iopamidol 370 mgI/ml, on renal function.
Secondary:
• To evaluate and compare the safety profile of iodixanol 320 mgI/ml and iopamidol 370 mgI/ml.
• To evaluate and compare the efficacy of iodixanol 320 mgI/ml and iopamidol 370 mgI/ml.</td></tr>
<tr><td colspan="3">Study Design: This was a multicentre, randomised, parallel-group, double-blind study in subjects with a combination of diabetes mellitus (Type I or II) and renal impairment. Subjects received either iodixanol 320 mgI/ml or iopamidol 370 mgI/ml as an intra-arterial injection. Safety was evaluated from changes in serum creatinine (SCr), the incidence of CM-induced nephropathy (CIN), changes in estimated glomerular filtration rate (eGFR) and the frequency and intensity of adverse events (AEs) up to Day 7. Efficacy was evaluated by assessing overall image quality and quality of diagnostic information.</td></tr>
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Selection of Subjects:

Inclusion criteria:

(1) The subject was over 18 years of age.
(2) The subject was referred for coronary angiography with or without PCI.
(3) The subject had diabetes mellitus I or II, treated with insulin or oral antiglycaemics for at least 1 year.
(4) The subject had renal impairment of non-acute aetiology: SCr measurement not older than 6 months ≥150 μmol/l (1.7 mg/dl) for men and ≥133 μmol/l (1.5 mg/dl) for women or a creatinine clearance (CrCl) ≤50 ml/min calculated according to Cockcroft-Gault formula.
(5) The subject was able and willing to comply with study procedures including hydration protocol and signed and dated (i.e., date and time) informed consent was obtained.
(6) The subject was male, or a female who was either surgically sterile (had had a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (cessation of menses for more than 1 year), or non-lactating, or if of childbearing potential the results of a serum or urine human chorionic gonadotropin pregnancy test, performed at screening, with the result known before investigational medicinal product (IMP) administration, was negative.

Exclusion criteria:

(1) The subject was previously included in the study.
(2) The subject had participated in any IMP study within 30 days prior to study enrolment.
(3) The subject had received iodinated contrast medium within 7 days before IMP administration or was scheduled to receive one within the study period.
(4) The subject was planned to undergo major surgery (coronary artery bypass graft, carotid endarterectomy, vascular surgery) within 3 days after the IMP administration.
(5) The subject was planned to undergo selective renal angiography.
(6) The subject had a history of serious hypersensitivity reaction to iodinated contrast media.
(7) The subject had severe liver or haematologic disease, multiple myeloma or manifest thyrotoxicosis.
(8) The subject had severe heart failure requiring intravenous therapy with diuretics, inotropes, and/or vasodilators.
(9) The subject was planned to receive an intravenous diuretic or intravenous mannitol in connection to the IMP administration.
(10) The subject was haemodynamically unstable pre-study (i.e., inability to sustain systolic blood pressure above 90 mmHg within 48 hours before IMP-administration without pressor or balloon support).
(11) The subject was on haemodialysis or peritoneal dialysis, and/or was in acute renal failure.
(12) The subject had undergone kidney transplantation.
(13) The subject had received or would receive any of the following potentially nephroprotective drugs within 3 days before or 3 days after IMP administration; N-acetylcysteine, fenoldopam, dopamine or hydration with sodium bicarbonate ($NaHCO_3$). Potentially nephroprotective drugs such as Ca-channel blockers, theophylline, etc. were allowed provided they were used for treatment of the subject's chronic underlying disease.
(14) The subject had received or was planned to receive any of the following nephrotoxic drugs within 7 days before or 3 days after IMP administration; aminoglycosides, vancomycin, amphotericin B, cyclosporin, methotrexate, cisplatin.
(15) The subject had received or was planned to receive nonsteroidal anti-inflammatory drugs (NSAID) within 3 days before or 3 days after IMP administration, with the exception of low doses of acetyl salicylic acid (up to 325 mg per day, and at a single occasion in connection with PCI up to 500 mg). However, subjects who were on a stable NSAID regimen could be enrolled.
(16) The subject had or was planned to have the initiation, discontinuation, or change in dose within 3 days before or 3 days after IMP administration of any of the following: trimethoprim, cimetidine, angiotensin

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converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB).

(17) The subject was on metformin (e.g., Glucophage™) at the time of coronary angiography/intervention. Metformin had to be discontinued according to local guidelines, and stopped no later than the time of IMP administration, withheld for at least 48 hours, until the subject's SCr had been evaluated and it was deemed safe to resume metformin.

Number of Subjects (planned and analysed): Initially, 306 evaluable subjects were planned for an adaptive interim analysis. The planned sample size was estimated to be 408 evaluable subjects which was to be adjusted based on the results of the initial analysis.
A total of 540 subjects were enrolled; 263 subjects received iodixanol, 263 subjects received iopamidol, 1 subject received both iodixanol and iopamidol and 13 subjects were not dosed. The per-protocol (PP) population was 418 evaluable subjects.

Treatment of Subjects:

- **Primary IMP:** Iodixanol 320 mgI/ml (VISIPAQUE™).
- **Comparator IMP:** Iopamidol 370 mgI/ml (Isovue™/Iopamiro™/Iopamiron™/Niopam™/ Scanlux™/ Solutrast™).
- **Administration Procedure:** Doses of IMP varied according to medical need. The examination procedure, including the IMP administration, was the same as routinely used in the hospitals. The CM, preheated to 37°C before administration, was injected intra-arterially. All subjects were well hydrated before, during, and after the examination, according to a standard hydration protocol.
- **Duration of Treatment:** IMP was administered at coronary angiography/PCI procedure only, followed by a 7-day safety follow-up period.

Endpoints
Safety:
Primary safety endpoints:

- Peak increase in SCr concentration from baseline up to Day 3.
- The incidence of CIN, defined as the number of subjects with an increase in SCr of at least 44 μmol/l (0.5 mg/dl) from baseline up to Day 3 (revised from 44.2 μmol/l as measurements were in whole numbers only).

Secondary safety endpoints:

- The number of subjects with an increase in SCr of at least 88 μmol/l (1.0 mg/dl) from baseline up to Day 3 (revised from 88.4 μmol/l as measurements were in whole numbers only).
- Change in eGFR from baseline up to Day 3, according to MDRD formula.
- Change in SCr from baseline up to Day 7.
- Frequency and intensity of AEs up to Day 7.

Efficacy:
Secondary efficacy endpoints:

- Overall image quality.
- Quality of diagnostic information.

Statistical Analyses
Primary safety analyses:

- Peak increase in SCr from baseline up to Day 3 was analysed by linear regression, and a two-sided 95% confidence interval (CI) for the difference in means between iodixanol and iopamidol was calculated.
- The incidence of CIN, defined as number of subjects with an increase in SCr of ≥44 μmol/l (0.5 mg/dl) from baseline up to Day 3, was analysed using logistic regression with covariates. A 95% CI for the odds ratio (OR) was calculated.

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Secondary safety analyses:

- The number of subjects with an increase in SCr of ≥88 µmol/l (1.0 mg/dl) from baseline up to Day 3 was analysed using logistic regression with covariates. A 95% CI for the OR was calculated.
- Change in eGFR, according to Modification of Diet in Renal Disease (MDRD) formula, from baseline up to Day 3 was analysed by linear regression, and a 95% CI for the difference in means between iodixanol and iopamidol was calculated.
- Change in SCr from baseline to Day 7 was analysed by linear regression, and a 95% CI for the difference in means between iodixanol and iopamidol was calculated.
- Differences in the proportion of subjects with one or more AEs (overall, related/unrelated to IMP, serious/non-serious) were tested using the two-sided Fisher's Exact test.

Secondary efficacy analyses:

- Overall image quality, assessed by means of a scoring system, was presented by frequency counts and percentages. The scores were tested by the two-sided Wilcoxon rank sum test to compare the two CM groups.
- The quality of diagnostic information was presented by frequency counts and percentages. Differences in the quality of diagnostic information were tested using the two-sided Fisher's exact test.

All linear and logistic regression analyses had CM group (iodixanol or iopamidol) and, for example, baseline SCr or baseline creatinine clearance (CrCl), age, and CM dose as covariates.

The primary safety analyses were based on the per protocol (PP) population. The PP population included all subjects who complied with the clinical study protocol sufficiently to ensure that the data were likely to exhibit the effects of the CM, i.e., all subjects with a pre-contrast (baseline) and at least one post-contrast SCr value on Days 2 or 3, without presence of any major protocol violations, and without evidence of other causes inducing acute renal dysfunction.

The sample size calculation was based on a two-sided Chi-square test, to test the hypothesis:

H_0: incidence of CIN iodixanol = incidence of CIN iopamidol

versus

H_1: mean incidence of CIN iodixanol ≠ mean incidence of CIN iopamidol

A sample size of 408 evaluable subjects (204 per CM group) would have 90% power to detect a difference in CIN rates between 6% in the iodixanol group and 16% in the iopamidol group, using a two-sided Chi-square test at a significance level of 0.05. Taking into consideration a drop-out rate of 10%, approximately 450 subjects needed to be included.

Summary of Results

Safety:

Peak increase in SCr from baseline to Day 3

In the PP population, the mean peak increase in SCr from baseline to Day 3 was 10.2 µmol/l. The mean peak increase in SCr up to Day 3 was 12.4 ± 33.8 µmol/l (min: -62, max: 336) for the iodixanol group and 7.9 ± 23.3 µmol/l (min: -53, max: 115) for the iopamidol group. One subject in the iodixanol group was a clear outlier in terms of peak increase in SCr (peak increase was 336). If this subject is excluded, the mean peak increase for the iodixanol group is 10.9 ± 25.6 µmol/l (min: -62, max: 133).

The primary analysis based on the total PP population results in a p-value of p=0.08 (not statistically significant) for the influence of the CM group, i.e., there was not a significant difference in mean peak increase in SCr in the iodixanol and iopamidol groups.

The 95% CI for the difference in means of 4.5 µmol/l between the groups (12.4 µmol/l in the iodixanol group and 7.9 µmol/l in the iopamidol group) is [-1.0, 10.1].

A post-hoc analysis was performed to investigate median peak increases in SCr. In the PP population, the median peak increase in SCr in the iodixanol arm was 9 µmol/l (0.10 mg/dl) while in the iopamidol arm it was

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8 μmol/l (0.09 mg/dl). The difference was not statistically significant when tested using the Wilcoxon rank sum test (p=0.13).

The incidence of CM-induced CIN from baseline to Day 3

In the total PP population there were 44 cases of apparent CIN (SCr increase of ≥44 μmol/l [≥0.5 mg/dl]); 24 cases in the iodixanol group and 20 cases in the iopamidol group. The overall incidence of CIN was 10.5%, 11.2% in the iodixanol arm and 9.9% in the iopamidol arm (p=0.7; 95% CI [-7.4, 4.6]). In 13 of these 44 cases (4 in the iodixanol group and 9 in the iopamidol group), the adjudication committee determined that other causes than CM administration had induced or significantly contributed to the increase in SCr.

The rate of CIN in which factors other than CM administration were unlikely contributing factors was 7.42% overall (31 of 418 subjects), 9.30% (20 of 215 subjects) in the iodixanol group and 5.42% (11 of 203 subjects) in the iopamidol group. These data were used for the primary CIN analyses.

The primary analyses based on the total PP population result in a p-value of p=0.13 (not statistically significant) for the influence of the CM group, i.e., there was not a significant difference in the incidence of CIN between the iodixanol and iopamidol groups. When this analysis was performed using a Chi-square test it resulted in a p-value of p=0.14 (95% CI [-1.2%, 8.9%]).

The OR of CIN for iopamidol in comparison to iodixanol is OR = 0.55, 95% CI [0.26, 1.20].

Of the 20 cases of CIN in the iodixanol group, 6 were borderline (SCr increased by 44 or 45 μmol/l), while none of the 11 cases in the iopamidol group were borderline (in all cases SCr increased by a minimum of 49 μmol/l). If these 6 'borderline' cases are excluded, the rate of CIN in the iodixanol group is 6.51%.

Subjects with an increase in SCr ≥88 μmol/l (1.0 mg/dl) from baseline up to Day 3

The percentage of subjects with an increase in SCr of ≥88 μmol/l) up to Day 3 was 3.26% (7 of 215) in the iodixanol group and 1.48% (3 of 203) in the iopamidol group. The resulting p-value for CM effect was p=0.18 (not statistically significant) for the influence of the CM group, i.e., there was not a significant difference in the incidence of increases in SCr of ≥88 μmol/l in the iodixanol and iopamidol groups. The OR of increases in SCr of ≥88 μmol/l for iopamidol in comparison to iodixanol was 0.38, 95% CI [0.09, 1.59].

Change in eGFR from baseline up to Day 3

The mean change in eGFR (according to the MDRD formula) from baseline up to Day 3 was -3.4 ml/min/1.73m^2 in the iodixanol group and -2.2 ml/min/1.73m^2 in the iopamidol group. The resulting p-value for CM effect in this linear regression model was p=0.09 (not statistically significant). The difference in mean change, not transformed, between iodixanol and iopamidol was -1.2, 95% CI [-2.94, 0.55].

Change in SCr from baseline to Day 7

On account of missing values, 365 observations were used for this analysis. The mean change in SCr from baseline up to Day 7 was 5.6 μmol/l in the iodixanol group and 3.6 μmol/l in the iopamidol group. The resulting p-value for CM effect in this linear regression model was p=0.45 (not statistically significant). The 95% CI for the difference (2.0) in mean change in SCr from baseline to Day 7 was [-3.27, 7.35].

Frequency and intensity of AEs

Of the 526 subjects in the AE population, 198 subjects (38%) experienced a total of 437 AEs. The majority of AEs were mild in intensity and resolved during the study. Thirty-one AEs in 26 subjects were considered related to IMP; 17 AEs in 15 subjects were suspected to be related to iodixanol and 14 AEs in 11 subjects were suspected to be related to iopamidol. There were 54 serious AEs (SAEs) reported (in 37 subjects) during the study. There were 7 withdrawals due to AEs/SAEs, 4 in the iodixanol group and 3 in the iopamidol group. Treatment was given for 313 AEs.

The most frequently affected body system for AEs was 'general disorders and administration site conditions'; 53 subjects (10%), of whom 28 subjects received iodixanol and 25 subjects received iopamidol, reported 66 AEs. Forty-eight subjects (9%) reported 65 AEs for 'gastrointestinal disorders', 37 subjects (7%) reported 48 AEs for 'cardiac disorders', 30 subjects (6%) reported 32 AEs for 'respiratory, thoracic and mediastinal

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disorders' and 29 subjects (6%) reported 30 AEs for 'vascular disorders'. For all remaining body systems, AEs were reported in no more than 25 (5%) subjects. For MedDRA preferred terms, the most frequently reported AE was 'nausea' (28 subjects).

The differences in the proportions of subjects with 1 or more AEs were tested using 2-sided Fisher's exact test. There was no difference between the treatment groups with respect to the proportion of subjects with 1 or more AEs (p=0.53).

Data on the frequency and intensity of AEs showed that both CM were similarly well tolerated, as did data on SAEs and deaths. The majority of AEs and SAEs in both CM groups were classified as being unrelated to the administration of CM and no unexpected serious or non-serious AEs were reported.

Efficacy:

Summary of overall image quality

For the 263 iodixanol subjects, overall image quality was rated as 'excellent' for 152 subjects (58%), 'good' for 100 subjects (38%), 'sufficient' for 10 subjects (4%), and 'insufficient' for 1 subject. For the 263 iopamidol subjects, it was rated as 'excellent' for 138 subjects (52%), 'good' for 115 subjects (44%), and 'sufficient' for 10 subjects (4%). A Wilcoxon rank sum test (2-sided) for CM-related differences in image quality was performed. The null hypothesis presented was that the study drug has no effect regarding the overall image quality, i.e., the image quality is independent of the CM used. There was no statistically significant difference in the overall image quality (p=0.41).

Summary of quality of diagnostic information

For the 263 iodixanol subjects, quality of diagnostic information was rated as 'optimal' for 258 subjects (98%) and 'suboptimal' for 5 subjects (2%). For the 263 iopamidol subjects, it was rated as 'optimal' for 262 subjects (100%) and suboptimal for 1 subject. A Fisher's exact test (2-sided) for CM-related differences in diagnostic information was performed. The null hypothesis presented was that the study drug has no effect regarding the quality of diagnostic information, i.e., the quality of diagnostic information is independent of the CM used. The null hypothesis was not rejected on the basis of the test result, meaning that no statistically significant difference was detected regarding the quality of diagnostic information obtained with iodixanol and iopamidol (p=0.22).

Conclusions: Data from this study indicate that both CM were generally well tolerated and efficacious in subjects with impaired renal function and diabetes mellitus who were undergoing coronary angiography with or without PCI. The data showed no statistically significant differences between the iodixanol and iopamidol groups in terms of mean peak increase in SCr or incidence of CIN from baseline to Day 3, which were the primary safety endpoints of the study. This lack of a significant difference is not proof of equivalence, as the trial was not designed with a non-inferiority endpoint in mind. Further, the results should be viewed in context of the fact that, on the basis of the results of the interim analysis, the sample size studied was too small to give the expected results.