Clinical Study Report Synopsis **GE Healthcare**
DXV406

Title: 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 mg I/mL (Visipaque™), with the non-ionic low osmolar contrast medium, iopamidol 300 mg I/mL, in subjects with impaired renal function and diabetes mellitus undergoing multidetector-row helical CT

This is an exact copy of the synopsis from the final clinical study report for the study DXV406. The final clinical study report (document-identifier: DXV406 CREP) was authorized for use on 26-Jul-2012 (Version 2.0).

<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:
VisipaqueTM
Isovue™/ Iopamiro™/ Iopamiron™/ Niopam™/ Solutrast™</td></tr>
<tr><td>Name of Active Ingredient:
Iodixanol
Iopamidol</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 mg I/mL (Visipaque™), with the non-ionic low osmolar contrast medium, iopamidol 300 mg I/mL, in subjects with impaired renal function and diabetes mellitus undergoing multidetector-row helical computed tomography</td></tr>
<tr><td colspan="3">Investigators and Study Centres: A total of 61 centres in America, Europe, and Asia recruited subjects for this study.</td></tr>
<tr><td colspan="3">Investigators and Centres for Independent Evaluation of Images: Not applicable.</td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Study Period: 01 June 2005 to 15 July 2011</td><td>Phase of Development: Phase 4</td></tr>
<tr><td colspan="3">Objectives:
Primary:
• To evaluate and compare the effects of two different contrast media (CM), iodixanol 320 mg I/mL and iopamidol 300 mg I/mL, on renal function
Secondary:
• To evaluate and compare the safety profile of iodixanol 320 mg I/mL and iopamidol 300 mg I/mL
• To evaluate and compare the efficacy of iodixanol 320 mg I/mL and iopamidol 300 mg I/mL</td></tr>
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Name of Active Ingredient: Iodixanol Iopamidol		

Study Design:

This was a multicentre, randomised, double-blind, parallel group, Phase 4 study to determine the renal effects of two different CM, the non-ionic iso-osmolar contrast medium (IOCM), iodixanol 320 mg I/mL, and the non-ionic low-osmolar contrast medium (LOCM), iopamidol 300 mg I/mL.

The target study population was subjects with a combination of diabetes mellitus type I or II treated with insulin or oral antidiabetic agents for at least 1 year and impaired renal function of non-acute aetiology who were referred for a contrast-enhanced multidetector-row helical computed tomography (MDCT) examination using a CM volume of at least 100 mL or at least 1.5 mL/kg bodyweight.

Safety was evaluated in terms of serum creatinine (SCr) changes, subject discomfort and incidence of adverse events (AEs). Efficacy was assessed by documenting image quality and quality of diagnostic information of the MDCT examination.

Selection of Subjects:

Inclusion Criteria:

(1) The subject was at least 18 years old.

(2) The subject had had diabetes mellitus (type I or II), treated with insulin or oral antidiabetic agents for at least 1 year.

(3) The subject had a pre-study SCr ≥1.7 mg/dL (150 µmol/L) if a man, or ≥1.5 mg/dL (133 µmol/L) if a woman, or an estimated pre-study estimated glomerular filtration rate (eGFR) ≤50 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) equation.*

The pre-study SCr value could not be older than 3 months and any acute causes of impaired renal function had to be ruled out.

*the four-component MDRD equation provides estimates of GFR standardised for body surface area, based on the variables SCr concentration, age, race, and sex:

eGFR (mL/min/1.73m2) = 186 x SCr-1.154 x age-0.203 (x 0.742 if female) (x 1.210 if black)

Pre-study SCr has to be expressed in milligrams per decilitre, age in years.

(4) The subject was referred for a contrast-enhanced MDCT examination, using a standardised CM volume of at least 100 mL or at least 1.5 mL per kilogram of body weight and an injection rate of between 2 and 5 mL/s. For subjects with a body weight exceeding 100 kg, a total CM volume of not greater than 150 mL (inclusive of any test bolus) was administered.

(5) The subject was a man, or a woman who was either surgically sterile (had had a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (with cessation of menses for more than 1 year), or, if of child-bearing potential, the result of a urine or serum β-human chorionic gonadotropin (β-HCG) pregnancy test conducted at screening was known to be negative before investigational medicinal product (IMP) administration.

(6) The subject was able and willing to comply with study procedures.

(7) Signed and dated (i.e., date and time) written informed consent was obtained.

Exclusion Criteria:

(1) The subject was pregnant or lactating.

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

(3) The subject had received another IMP within 30 days before or was scheduled to receive one within 7 days after IMP administration.

(4) The subject had received intravascular or intrathecal administration of iodinated CM within 7 days before or would receive one within 3 days after IMP administration.

(5) The subject has a history of serious hypersensitivity reaction to iodinated CM.

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(6) The subject had non-compensated heart failure (NYHA III or IV).
(7) The subject had manifest thyrotoxicosis.
(8) The subject was in acute renal failure or in acute on chronic renal failure.
(9) The subject had undergone kidney transplantation.
(10) The subject was on haemodialysis or peritoneal dialysis.
(11) The subject had liver cirrhosis with ascites.
(12) The subject had multiple myeloma.
(13) The subject was haemodynamically unstable pre-study.
(14) The subject was scheduled for major surgery within 3 days after IMP administration.
(15) The subject had received or would receive any of the following potentially nephroprotective drugs from 3 days before until 7 days after IMP administration: n-acetylcysteine, fenoldopam, dopamine, or hydration with sodium bicarbonate. Concurrent medication with other drugs that were potentially nephroprotective, like calcium channel blockers or theophylline, was permitted provided they were used for the subject's underlying disease (e.g., cardiac disease, arterial hypertension, bronchial asthma).
(16) 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, cyclosporine, tacrolimus, methotrexate, cisplatin.
(17) The subject had received nonsteroidal anti-inflammatory drugs (NSAID) within 3 days before or would receive such drugs within 7 days after IMP administration, with the exception of low dose aspirin (up to 325 mg per day). However, subjects who were on a stable NSAID regimen could be enrolled.
(18) The subject had had or was planned to have the initiation, discontinuation, or change in dose of any of the following from 3 days before until 7 days after IMP administration: trimethoprim, cimetidine, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers.
(19) The subject was on metformin treatment at the time of the study procedure: metformin administration had to be discontinued prior to IMP administration, according to local guidelines and withheld for at least 48 hours. Metformin could be resumed once the subject's SCr had been evaluated 3 days post-procedure, and it was deemed safe to do so by the investigator.

Number of Subjects (planned and analysed):

Planned

A total of approximately 720 subjects were planned to be enrolled in this study in order to obtain 428 evaluable subjects for the primary per-protocol (PP) safety analysis (incidence rate of CM-induced nephropathy [CIN] between the 2 groups). In the subsequent protocol amendment, it indicated that the number of subjects enrolled into the study could be updated following an informal interim analysis of the incidence of CIN in the 2 groups.

Actual

The study was terminated by the Sponsor after enrolling 656 subjects. Of these, 321 subjects received iodixanol, 327 subjects received iopamidol, 7 subjects did not receive either contrast agent, and 1 subject received unknown contrast type.

Treatment of Subjects

Investigational Medicinal Product: Iodixanol 320 mg I/mL (Visipaque^{TM})

Comparator (also referred to as IMP in the text below): Iopamidol 300 mg I/mL (trading as Isovue™/ Iopamiro™/ Iopamiron™/ Niopam™/ Solutrast™)

Dose: At least 1.5 mL/kg body weight or a minimum of 100 mL (inclusive of any test bolus dose and in compliance with local Summary of Product Characteristics) was given. For subjects with a body weight exceeding 100 kg, a total CM volume of not greater than 150 mL (inclusive of any test bolus dose) was administered.

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Mode of Administration: Intravenous bolus injection at an injection rate of between 2 and 5 mL/s. All subjects were well hydrated before, during, and after the CT examination, according to a standard hydration protocol.
Duration of Treatment: Single dose administration, 7 days safety follow-up period.

Endpoints
Safety:
Primary safety endpoint
Incidence rate of CIN, defined as an intra-individual increase in SCr of at least 44.2 µmol/L (0.5 mg/dL) from baseline up to day 3

Secondary safety endpoints
- Peak increase in SCr from baseline up to day 3
- Number of subjects with an increase in SCr of at least 88.4 µmol/L (1.0 mg/dL) from baseline up to day 3
- Change in SCr from baseline to day 7
- Frequency and intensity of injection-associated discomfort
- Frequency and intensity of AEs

Efficacy:
Secondary efficacy endpoints
- Overall image quality
- Quality of diagnostic information

Statistical Analyses:
The primary endpoint was analysed by logistic regression. For simplification purposes, however, the Fisher's Exact test was applied for the sample size calculation. Assuming that the power of the Fisher's Exact test was a good approximation for the power of the logistic regression model, the Fisher's Exact test was considered a suitable basis for the sample size calculation.

The primary safety analysis was based on the PP population. The PP population included all subjects from the target study population who complied with the study protocol sufficiently to ensure that the data were likely to exhibit the effects of the IMP, i.e., all subjects with a pre-contrast (baseline) SCr value of ≥1.5 mg/dL for males and ≥1.3 mg/dL for females or eGFR of ≤50 mL/min/1.73 m^2 and a post-contrast SCr value available on days 2 or 3, administered ≥100 mL or 1.5 mL/kg bodyweight IMP, without presence of any major protocol violations, and without evidence of other causes inducing acute renal dysfunction.

Primary safety analysis
The primary endpoint, the incidence rate of CIN defined as percentage of subjects with an increase in SCr of at least 44.2 µmol/L (0.5 mg/dL) from baseline up to day 3, was analysed by logistic regression, together with a 95% confidence interval for the odds ratio between the two IMP groups.

Secondary safety analysis
- The peak increase in SCr from baseline up to day 3 was analysed by linear regression. In addition, a 95% confidence interval for the difference in means between the two IMP groups was presented.
- The number of subjects with an increase in SCr of at least 88.4 µmol/L (1.0 mg/dL) from baseline up to day 3 was analysed by logistic regression, together with a 95% confidence interval for the odds ratio between the two IMP groups.
- The change in SCr from baseline to day 7 was analysed by linear regression. In addition, a 95% confidence interval for the difference in means between the two IMP groups was presented.
- Differences in the proportion of subjects with injection-associated discomfort in the 2 IMP groups and

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differences in intensity of injection-associated discomfort were tested using two-sided Fisher's Exact test.

- Differences in the proportion of subjects with 1 or more AEs (overall, related to IMP or not, serious or non serious) were tested using two-sided Fisher's Exact test.

Secondary efficacy analysis

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

Interim analysis

An interim analysis was performed during this study following a protocol amendment and development of a specific statistical analysis plan for the interim analysis. No data cleaning was performed. Initially, the interim analysis was to determine the CIN rate for each contrast group using Group A versus Group B designation without breaking the study blinding. The results of this interim analysis were intended to be used to decide whether or not to continue the study according to a pre-defined decision tree in the protocol. A total of 632 subjects were enrolled at the time of the interim analysis. Of these, 594 subjects had received a dose of study medication, had serum creatinine values at baseline and post-baseline, and were therefore included in the intent-to-treat (ITT) population; 426 subjects had a baseline serum creatinine value ≥1.5 mg/dL for males and ≥1.3 mg/dL for females or eGFR of ≤50 mL/min/1.73 m2 and a post-contrast serum creatinine value available on days 2 or 3 and administered ≥100 mL or ≥1.5 mL/kg bodyweight IMP, and were therefore included in the per-protocol (PP) population (with 206/220 subjects in treatments A/B). The difference of CIN rate between Group A and Group B was 4% in ITT population analysis and 5% in PP population analysis without clear direction of the difference between the treatment and the control group.

Subsequently, a Data Monitoring Committee (DMC) was formed to break the study blinding and to perform additional exploratory analyses. The DMC found that the iodixanol group showed an increased rate of CIN in some analyses and no differences in other analyses as compared to the iopamidol group, which would result in a recommendation of stopping the study if the sponsor had not made the termination decision.

Analysis Populations*:*

Data analysis in this study was performed based on 4 different patient populations defined as follows.

ITT population: All subjects included in the study and allocated to an IMP group. The subjects were followed up, assessed and analysed as members of that IMP group irrespective of their compliance to the planned course of treatment.

Overall safety population: All subjects included in the study and who received one of the IMPs. The subjects were analysed for the occurrence of injection-associated discomfort and AEs, according to the IMP that they received.

Efficacy population: All subjects included in the study, receiving one of the IMPs, and for whom efficacy assessments were available. The subjects were analysed for the secondary efficacy endpoints.

PP population: All subjects from the target study population who complied with the study protocol sufficiently to ensure that the data were likely to exhibit the effects of the IMP, i.e., all subjects with a pre-contrast (baseline) SCr value ≥1.5 mg/dL for males and ≥1.3 mg/dL for females or eGFR of ≤50 mL/min/1.73 m^2 and a post-contrast SCr value available on days 2 or 3, administered ≥100 mL or ≥1.5 mL/kg bodyweight IMP, without presence of any major protocol violations, and without evidence of other causes inducing acute renal

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dysfunction. Analysis of the primary study endpoint was based on the PP population.

Summary of Results

A total of 648 subjects consisting of overall safety and efficacy populations were included in the final analysis. Of them, 399 subjects were included in the PP population; 192 subjects received iodixanol and 207 subjects received iopamidol. The majority of exclusions from the PP population were because a subject did not have a pre-contrast (baseline) SCr value of ≥1.5 mg/dL for males and ≥1.3 mg/dL for females or eGFR of ≤50 mL/min/1.73m^2 (202/249 subjects, 81.1%).

For the PP population, there were similar numbers of males (210/399, 52.6%) and females (189/399, 47.4%). Subjects were predominantly Caucasian (306 subjects, 76.7%). Age ranged from 29 to 88 years, with a mean (±SD) of 66.1 (±11.79) years. Mean (±SD) height, weight and body mass index of the subjects were 167.4 (±9.44) cm, 82.0 (±18.80) kg and 29.2 (±6.06) kg/m^2, respectively. There were no notable differences between the iodixanol and iopamidol groups.

For other baseline characteristics, including baseline SCr and eGFR values, duration and type of diabetes mellitus, prior exposure to iodinated contrast agents, hydration status, and volume of contrast administered for the CECT procedure, there were also no notable differences between the iodixanol and iopamidol groups.

The final data analyses were performed based on the clean data. The primary and secondary safety endpoints related to CIN or change of SCr post-contrast administration were analysed based on the PP population. The analysis of overall safety and injection-associated discomfort was based on the safety population. The efficacy analysis was based on the efficacy population.

The key study results are presented as follows.

The table below presents the primary and secondary safety endpoints related to CIN or change of SCr post-contrast administration.

Safety Endpoints		**Iodixanol 320 mg I/mL N=192; n (%)**	**Iopamidol 300 mg I/mL N=207; n (%)**	**p-value**
Primary	CIN (≥0.5 mg/dL increase from baseline)	19 (9.9)	22 (10.6)	0.590
Secondary	Peak SCr Increase to Day 3	0.148	0.130	NS
	CIN (≥1.0 mg/dL increase from baseline)	5 (2.6)	7 (3.38)	0.611
	SCr change from baseline to Day 7	0.057	0.033	NS

Analysis of the primary safety endpoint, incidence rate of CIN, defined as an intra-individual increase in SCr of at least 44.2 µmol/L (0.5 mg/dL) from baseline up to day 3, showed no statistically significant differences between the treatment groups (p = 0.590).

In the analysis of the secondary safety endpoints related to CIN or change of SCr after contrast administration, no statistically significant differences between treatment groups were identified for peak increase in SCr from baseline up to day 3, number of subjects with an increase in SCr of at least 88.4 µmol/L (1.0 mg/dL) from baseline up to day 3, and change in SCr from baseline to day 7.

In the overall safety analysis, the frequency and intensity of injection-associated discomfort was also similar across treatment groups, with the exception that a greater proportion of subjects in the iopamidol treatment

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group reported moderate or severe intensity of warmth/heat compared to the iodixanol group (p=0.039).

The frequency of TEAEs between iodixanol and iopamidol groups were also similar (13.7% [44/321] vs. 12.2% [40/327]), as were the frequency of treatment-emergent serious adverse events (SAEs) (1.9% [6/321] vs. 1.8% [6/327]) and deaths (0.9% [3/321] vs. 1.2% [4/327]). However, a statistically significantly higher proportion of TEAEs was thought to be related to IMP for the iodixanol group than for the iopamidol group (p=0.043). This finding was primarily related to the higher incidence of 'rash' in the iodixanol group (9 subjects, 2.8%) than in the iopamidol group (3 subjects, 0.9%) (p=0.087).

Image quality and the quality of diagnostic information were comparable for both iodixanol and iopamidol as summarised in the following table.

Efficacy Endpoints		**Iodixanol 320 mg I/mL N= 321; n (%)**	**Iopamidol 300 mg I/mL N=327; n (%)**	**p-value**
Overall Image Quality	Excellent	220 (68.5)	207 (63.3)	0.221
	Good	81 (25.2)	103 (31.5)	
	Sufficient	13 (4.0)	9 (2.8)	
	Insufficient	7 (2.2)	8 (2.4)	
Quality of Diagnostic Information	Optimal	299 (93.1)	305 (93.3)	1.000
	Suboptimal	20 (6.2)	20 (6.1)	
	Not Diagnostic	2 (0.6)	2 (0.6)	

Conclusions:

In summary, in this multicentre, randomised, double-blind, parallel group, Phase 4 study, the results showed that:

- There was no statistically significant difference in primary CIN rate or increase in CIN rate of at least 88.4 µmol/L (1.0 mg/dL) from baseline up to day 3 between the treatment groups.
- There was no difference in peak SCr increase from baseline to day 3 or SCr change from baseline to day 7 between the treatment groups.
- For other secondary endpoints, there were similar occurrences of injection-associated discomfort, however more subjects in the iopamidol group experiencing warmth of moderate or severe intensity.
- Frequency and intensity of AEs showed that iodixanol and iopamidol were similarly well tolerated, as did data on SAEs and deaths; however, a statistically significantly higher proportion of AEs were thought to be related to IMP for the iodixanol group than for the iopamidol group due to a higher incidence of 'rash' in the iodixanol group than in the iopamidol group.
- The overall image quality and quality of diagnostic information indicated that both iodixanol and iopamidol were very well suited for CECT examination.

In conclusion, in this study as designed, the safety and efficacy profiles of iodixanol 320 mg I/mL and iopamidol 300 mg I/mL were generally similar.