CONFIDENTIAL

Enhancement of the Lower Extremities Computed Tomography: Iomeron® 400 vs. Visipaque™ 320 (ELECTIV)

This was a parallel-group comparison of Iomeron® 400 and Visipaque™ 320 in subjects with mild-to-moderate renal impairment who underwent clinically-indicated intravenous contrast-enhanced multidetector computed tomography angiography (MDCTA) scanning of the lower extremity arterial system.

Name of Test Agent:	Iomeron® (iomeprol)
Protocol No.:	IOM-115
Developmental Phase of Study:	Phase IV
Study Initiation Date (first subject enrolled):	08 August 2005
Study Completion Date (last subject completed):	16 August 2005
Summary Date:	26 September 2006
Sponsor:	Bracco S.p.A. Group Medical Affairs Via Folli 50 20134 Milan, Italy
Sponsor's Responsible Medical Officer:	Alberto Spinazzi, MD Bracco Group
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The study described in this report was performed in compliance with Good Clinical Practice (GCP).

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Title of Study: Enhancement of the Lower Extremities Computed Tomography: Iomeron® 400 vs. Visipaque™ 320 (ELECTIV) (Protocol IOM-115)

Investigators/Study Center(s): This study was intended to be a multicenter trial with approximately 120 subjects enrolled in Europe. After only 1 subject was enrolled by [redacted], the study was prematurely terminated by the Sponsor due to the difficulty of recruitment.

Publication (reference, if any): None

Study Period: First subject enrolled: 08 August 2005 Last subject completed: 16 August 2005	**Phase of Development:** IV

Objectives:
The primary objective of this study was:

- To quantitatively compare the efficacy of enhancement of key arteries in subjects with mild-to-moderate renal impairment (serum creatinine [SCr] = 1.5 to 2.5 mg/dL and/or calculated creatinine clearance [CrCl] = 10 to 60 mL/min) who underwent clinically-indicated intravenous contrast-enhanced multidetector computed tomography angiography (MDCTA) scanning of the lower extremity arterial system with equi-iodine doses of 1 of 2 contrast agents, Iomeron® 400 or Visipaque™ 320.

The secondary objectives of this study were:

- To qualitatively compare the efficacy of enhancement in subjects, both overall and at a segmental/regional level, with mild-to-moderate renal impairment (SCr = 1.5 to 2.5 mg/dL and/or calculated CrCl = 10 to 60 mL/min) who underwent clinically-indicated intravenous contrast-enhanced MDCTA scanning of the lower extremity arterial system with equi-iodine doses of 1 of 2 contrast agents, Iomeron® 400 or Visipaque™ 320.
- To compare between the 2 investigational products the incidence of contrast-induced nephropathy (CIN), defined as a $\geq$0.5 mg/dL post-CT scan increase in SCr at 48 to 72 hours postdose vs. predose value.
- To compare between the 2 investigational products the incidence of delayed (2 hours to 7 days post-administration) hypersensitivity-type cutaneous/subcutaneous adverse reactions.

Study Design: This was a Phase IV, multicenter, randomized, double-blind, parallel-group comparison study of Iomeron® 400 and Visipaque™ 320 in subjects with mild-to-moderate renal impairment (SCr = 1.5 to 2.5 mg/dL and/or calculated CrCl = 10 to 60 mL/min) who underwent clinically-indicated intravenous contrast-enhanced MDCTA scanning of the lower extremity arterial system. Approximately 120 subjects were to be enrolled in this study in Europe.

Subjects were to be randomized to receive equi-iodine doses (40 g) of Iomeron® or Visipaque™ intravenously via power injector plus a chaser of saline solution of 20 mL at the same injection rate of 5 mL/sec. Each subject was to be evaluated for the incidence of CIN at 48 to 72 hours postdose. If a subject had an increase of ≥0.5 mg/dL in SCr from baseline at 48 to 72 hours postdose, the SCr level was to be re-evaluated on Day 7. The monitoring of adverse events began when the Informed Consent Form was signed and the subject was enrolled into the study, and continued for 2 hours postdose. Delayed hypersensitivity-type adverse reactions were collected from 2 hours to 7 days postdose.

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Study Design (continued): Efficacy evaluations of the image datasets were to be evaluated both quantitatively and qualitatively by 3 off-site blinded readers. A single on-site qualitative blinded reading was also to be performed for each image dataset. However, due to the early termination of this study, no off-site assessments were conducted.

Subject Population:
Number of Subjects Planned: 120
Number of Subjects Enrolled: 1
Number of Subjects Randomized: Visipaque™ 320, 1 subject
Number of Subjects Dosed: Visipaque™ 320, 1 subject
Number of Subjects Evaluated for Efficacy (On-site): Visipaque™ 320, 1 subject
Number of Subjects Evaluated for Safety: Visipaque™ 320, 1 subject

Diagnosis and Main Criteria for Inclusion: A subject was enrolled in the study if the subject met the following inclusion criteria: provided written informed consent and was willing to comply with protocol requirements; was ≥18 years of age; had a stable baseline SCr level = 1.5 to 2.5 mg/dL and/or calculated CrCl = 10 to 60 mL/min documented within 2 weeks of investigational product administration that met the inclusion criteria and was consistent with a previous result available within 6 months of dosing; however, if the subject only had 1 SCr and/or calculated CrCl result available within a 6-month period, to qualify for the study, the subject had to have blood drawn for SCr within 72 hours of dosing; was referred for a clinically-indicated contrast-enhanced MDCTA examination of the lower extremity arterial system.

A subject was excluded from the study if the subject did not fulfill the inclusion criteria, or if any of the following conditions were observed: determined by their physician that prophylactic medication was medically required in order to receive intravascular administration of an iodinated contrast agent; had a history of hypersensitivity to iodine-containing compounds; had severe congestive heart failure (Class III or IV in accordance with the classification of the New York Heart Association); suspected of having hyperthyroidism or thyroid malignancies; underwent any other radiological procedure utilizing X-ray contrast media from 72 hours before to 7 days after the administration of the investigational product; had uncontrolled diabetes; was on dialysis; had unstable renal function/SCr levels/acute renal failure; was a pregnant or lactating female (possibility of pregnancy was excluded by laboratory testing on-site at the institution [measurement of serum or urine beta human chorionic gonadotropin (βHCG)] within 72 hours prior to the start of investigational product administration or by history [e.g., tubal ligation or hysterectomy, post menopausal with a minimum 1 year without menses]); had been previously entered in this study or had received an investigational compound within 30 days prior to admission to this study; had any medical condition or other circumstances that would significantly decrease the chances of obtaining reliable data or achieving the study objectives, i.e., seen to have had a drug dependence or seen to have had psychiatric disorders, dementia, or other reasons for expected poor compliance with the instructions of the Investigator.

Dose and Mode of Administration, Batch Number of Test Agent: Iomeron® 400 was to be administered intravenously at a volume of 100 mL, corresponding to 40 g of iodine. The injection rate was to be 5 mL/sec. Batch No. [redacted]).

Dose and Mode of Administration of Comparative Agent: Visipaque™ 320 was administered intravenously at a volume of 125 mL, corresponding to 40 g of iodine. The injection rate was 5 mL/sec. Batch No. [redacted].

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Duration of Treatment: The MDCTA examinations associated with administration of the contrast agent were completed within approximately 1 hour. The monitoring of adverse events began when the Informed Consent Form was signed and the subject was enrolled into the study, and continued for 2 hours postdose. Delayed hypersensitivity-type adverse reactions were collected from 2 hours to 7 days postdose. For evaluation of CIN, subjects needed to provide a blood sample within 72 hours predose, at 48 to 72 hours postdose, and, if needed, again at 7 days postdose, to obtain SCr levels.

Evaluation Parameters:

Efficacy:
The CT images for each subject were to be evaluated both quantitatively and qualitatively on-site and off-site. However, due to the early termination of this study, no off-site assessments were conducted. The on-site reader blinded to dose and contrast agent administered was first asked whether the imaging examination was technically adequate for assessment. If the images were technically inadequate, the reader checked all that applied (1 = subject motion makes the examination uninterpretable; 2 = poor technique was used to acquire the examination; 3 = subject's anatomy of interest was not captured by the examination; 4 = other [specify]) and did not proceed with any further assessments. Additionally, the reader evaluated whether there were motion artifacts present. If present, they were to be scored (1 = minimal artifacts present [not compromising the evaluation of images]; 2 = substantial artifacts present [compromising the evaluation of images]). For the qualitative evaluation, a formal 5-level grading scale (1 = poor; 2 = insufficient; 3 = fair; 4 = good; 5 = excellent) was used. Each entire subject image dataset was given a single numerical grade of 1 to 5.

Safety:

Safety was assessed by:

- SCr level measurements at baseline, 48 to 72 hours postdose, and 7 days postdose, where applicable.
- Incidence of CIN, defined as a ≥0.5 mg/dL increase in SCr at 48 to 72 hours postdose compared to baseline.
- Change in clinical renal status of the subject, specifically including any notation of the onset of renal dialysis, or of death.
- Incidence of delayed hypersensitivity reactions.
- Adverse events.
- Change in heart rate.

Statistical Methods:

Demographics and Baseline Characteristics: Demographic and baseline characteristics were listed for each subject.

Efficacy and Safety: No statistical analyses were performed; data are provided in ad hoc listings.

Summary and Conclusions:

Demographics:
The 1 subject enrolled in this study was a 66-year-old White male. His height and weight were 190 cm and 105 kg, respectively.

Exposure to Investigational Product and/or Comparator Product:
The 1 subject enrolled in this study received the 125 mL of Visipaque™ 320 prescribed in the protocol.

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Summary and Conclusions (continued):

Efficacy:
Due to the early termination of this study, no efficacy parameters were analyzed.

Safety:
No adverse events were reported in this study.

Conclusions:
Due to the early termination of this study, and the enrollment of only 1 subject, no conclusions can be drawn.

Date of Summary: 26 September 2006