CONFIDENTIAL

A Double-Blind Inter-Individual Comparison of Iomeprol 300 and Iomeprol 400 in the Assessment of Perfusion CT of Advanced Renal Carcinoma

Name of Test Agent:	Iomeron® (iomeprol injection)
Protocol No.:	IOM/BRA/037
EudraCT No.:	2006-002858-29
Developmental Phase of Study:	IV
Study Initiation Date (first subject enrolled):	18 September 2007
Study Completion Date (last subject completed):	15 September 2009
Clinical Trial Report Date:	Final 29 October 2010 (Abbreviated Report)

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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: A Double-Blind Inter-Individual Comparison of Iomeprol 300 and Iomeprol 400 in the Assessment of Perfusion CT of Advanced Renal Carcinoma (Protocol IOM/BRA/037)

Investigators/Study Center(s):
Two study centers in Germany.
Center 1: [redacted]
Center 2: [redacted]

Publication (reference, if any): None

Study Period: First subject enrolled: 18 September 2007 Last subject completed: 15 September 2009 Off-site assessment: Not applicable	**Phase of Development:** IV

Objectives:

Primary:

The primary objective was to quantitatively compare the enhancement properties in perfusion computed tomography (CT) between injection protocols using a high iodine flux [gI/s] with Iomeprol 400 and a lower iodine flux with Iomeprol 300, at equal injection rates [mL/s].

The maximum enhancement of the contrast bolus in the abdominal aorta (= arterial input function) was to be analyzed. The maximum enhancement was to be defined as the increase of contrast density [Hounsfield units, HU] from baseline. This value was to serve as a performance parameter of the arterial input function, which consequently influences the overall perfusion assessment.

Secondary:

- To compare between the Iomeprol 300 and Iomeprol 400 injection protocols:
  - Contrast enhancement [HU] and signal-to-noise indices in normal organ and tumor tissues, in CT perfusion images, and in venous phase CT images;
  - Contrast dynamics in terms of slope [HU/s], slope to maximum enhancement, maximum initial slope [HU/s], the time after start of contrast injection to maximum enhancement [s], the rise time to maximum [s], as well as the integral of enhancement over time [HUs] of enhancement time curves obtained separately for all regions of interest (ROIs);
  - Calculated perfusion parameters (absolute values and standard deviation [SD]), and signal-to-noise indices (value/SD);
  - Qualitative evaluations of tumor opacification and diagnostic adequacy of parameter maps.
- To correlate the calculated perfusion parameters with the subsequent change of tumor size (treatment effect) in follow-up examinations.

Study Design:
Multi-center, randomized, double-blind parallel-group comparison.
The study was planned to run for 3 years from first patient in to last patient out, including a 3-month follow-up examination.

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Subject Population:
Number of Subjects Planned: 60 (48 evaluable patients)
Number of Subjects Enrolled: 18
Number of Subjects Randomized: 17
Number of Subjects Dosed: 17 (Iomeprol 300: N= 7; Iomeprol 400: N=10)
Number of Subjects Evaluated for Efficacy: 0
Number of Subjects Evaluated for Safety: 17

Change of Conduct:
The study was terminated prematurely due to slow enrollment. It was decided to collect and analyze selected data only (see section on statistical methods).

Diagnosis and Main Criteria for Inclusion:
Adult patient (age: ≥35 years) diagnosed with renal carcinoma with at least 1 abdominal mass larger than 2 cm and an indication for CT due to re-staging before the start of a new antiangiogenic treatment.

Dose and Mode of Administration, Batch Number of Test Agent:
50 mL of Iomeprol 400 (Iomeron® 400; [redacted]; expiry date: [redacted]) were injected intravenously at an injection rate of 5 mL/s, immediately followed by an injection of 30 mL at a rate of 1 mL/s. This corresponded to a total injection duration of 40 s. The maximum iodine flux was 2 gI/s (total iodine amount: 32 gI). Contrast agent injection was followed by a 20 mL flush of physiological saline (0.9% NaCl solution) injected at a rate of 1 mL/s.

Dose and Mode of Administration of Comparative Agent:
50 mL of Iomeprol 300 (Iomeron® 300; [redacted]; expiry date: [redacted]) were injected intravenously at an injection rate of 5 mL/s, immediately followed by an injection of 30 + 27 mL at a rate of 1 mL/s. This corresponded to a total injection duration of 67 s. The maximum iodine flux was 1.5 gI/s (total iodine amount: 32 gI). Contrast agent injection was followed by a 20 mL flush of physiological saline (0.9% NaCl solution) injected at a rate of 1 mL/s.

Duration of Treatment:
This was a single dose study. The study duration for each patient was 1 day. The duration of the CT examination (perfusion CT followed by diagnostic venous phase) was approximately 15 minutes. Close safety monitoring was performed from the time of signing the Informed Consent until 2 hours after administration of contrast agent. A telephone follow-up was to be performed 24 hours after the injection of the contrast agent.

Evaluation Parameters (as planned in the study protocol):
Efficacy
Perfusion CT:

- Technical adequacy of primary axial perfusion image;
- Quality of tumor opacification;
- Diagnostic adequacy of standardized color-coded perfusion maps;
- Quantitative evaluations:
  ROIs: abdominal aorta, psoas muscles, normal renal tissue, tumor tissue
  - Size of ROI (diameter in [mm]);
  - Contrast density [HU] (mean and SD) at baseline (3 successive measurements);
  - Contrast density [HU] (mean and SD) at maximum;

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Evaluation Parameters (continued):

Quantitative evaluations (continued):

- Contrast density [HU] (mean and SD) at late phase of perfusion CT (3 latest measurements);
- Time after start of contrast injection to start of enhancement [s] and to maximum enhancement [s] (time required from start of enhancement to maximum was defined as rise time [s] of the contrast enhancement);
- Slope to maximum [HU/s] (= slope from start of increase to maximum), and total slope of curve to late phase (= slope from start of increase to 40 s after contrast agent injection) of the contrast density time curves.

Non-vascular ROIs

- Perfusion [mL/100mL·min] (mean and SD);
- Permeability [mL/100mL·min] (mean and SD);
- Regional blood volume [mL/100mL] (mean and SD).

Data centrally derived from fitted curves

- The integral of enhancement over time above baseline [HUs] from start of enhancement to late phase (40 s) of all ROIs;
- The maximum initial slope (values [HU/s] and quality parameters of the fitted curve) of the contrast density time curves of all ROIs;
- The full-width-half-maximum [s], and its corresponding integral of enhancement [HUs] from original arterial input functions.

Venous Phase CT:

- Technical adequacy of venous phase CT images;
- Study target lesions:
  - Largest diameter [mm] and largest perpendicular diameter [mm] in the axial plane;
  - Largest z-axis diameter [mm] in the coronal plane.
- RECIST target lesions (up to 10, including study target lesion):
  - Number of lesion;
  - Location of lesion;
  - Largest diameter [mm].
- Contrast density measurements [HU] (mean and SD):
  - Size of the ROIs (diameter in [mm]).

Diagnosis and treatment:

- Radiological and histological diagnosis (grading and staging);
- Antiangiogenic drug, other treatments, dose, treatment duration.

Follow-up examinations:

- Documentation of the follow-up examination (modality, scanner type, examination sequence);
- Study target lesion:
  - Largest axial diameter [mm], and its largest perpendicular diameter [mm];
  - Largest z-axis diameter [mm] in the coronal plane;
- RECIST target lesions (number, location, largest diameter [mm]);
- RECIST response for the level of target lesions.

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Evaluation Parameters (continued):

Safety

Patients were monitored for untoward medical occurrences starting at the time of Informed Consent until 24 hours after administration of investigational product.

Statistical Methods:

Statistical methods were specified in an abridged statistical analysis plan (SAP). As no efficacy data were collected, the abridged SAP did not stipulate an analysis of efficacy (in contrast to the planned statistical analysis as described in the study protocol).

No statistical testing was performed. Selected data were analyzed by descriptive statistics. Frequency distribution tables (number, %) were produced for categorical data and summary statistics (number, mean, SD, median, minimum, maximum) for continuous data.

Demographics and Baseline Characteristics:

Summary tables were provided for the number of subjects who had been enrolled, randomized, and dosed, and for subjects who had received the investigational product but did not complete the study. Summary tables were provided for demographic and baseline characteristics, including age, sex, race, height, and weight. Details on concomitant medications were presented in data listings.

Exposure to Radiation and Exposure to Investigational Product:

The date of the perfusion CT and the CT dose index were presented in data listings. The injected volumes of investigational product per phase and injection rates were summarized by category in frequency tables. Details on investigational product administration were listed.

Safety:

Safety analysis included all subjects dosed with the investigational product (SAF population) and was based on the analysis of adverse events.

Summary and Conclusions:

Disposition:

Two patients in the Iomeprol 300 group did not complete the core part of the study after dosing: Patient #[redacted] (no residual disease) and Patient #[redacted] (technical protocol violation). Protocol deviations were documented for 3 patients in the Iomeprol 300 group (entrance criteria not met, wrong CT scanner used, technical protocol violation) and for 4 patients in the Iomeprol 400 group (all: wrong CT scanner used). The 3-months follow-up examination was not performed for any patient.

Demographics:

The study patients were white with the exception of 1 Asian patient in the Iomeprol 300 group. More male than female patients participated in the study. The Iomeprol 300 group comprised 5 (71.4%) male and 2 (28.6%) female patients, and the Iomeprol 400 group 6 (60.0%) male and 4 (40.0%) female patients. The mean age of the patients was 66.7 ± 16.7 years in the Iomeprol 300 group and 66.0 ± 14.1 years in the Iomeprol 400 group. The mean weight was 73.0 ± 6.6 kg (Iomeprol 300) and 78.7 ± 13.3 kg (Iomeprol 400), respectively. The mean height of the Iomeprol 300 patients was 169.4 ± 9.2 cm and the mean height of the Iomeprol 400 patients was 171.0 ± 6.4 cm.

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Demographics (continued):

	Iomeprol 300 (N = 7)	Iomeprol 400 (N = 10)		Iomeprol 300 (N = 7)	Iomeprol 400 (N = 10)
Gender, n (%)			**Height, cm**		
Male	5 (71.4)	6 (60.0)	Mean (SD)	169.4 (9.2)	171.0 (6.4)
Female	2 (28.6)	4 (40.0)	Range	155, 178	163, 183
Age, yr			**Race, n (%)**		
Mean (SD)	66.7 (16.7)	66.0 (14.1)	White	6 (85.7)	10 (100.0)
Range	36, 88	37, 83	Black	0	0
Weight, kg			Asian	1 (14.3)	0
Mean (SD)	73.0 (6.6)	78.7 (13.3)	Other	0	0
Range	64, 85	65, 110			

Concomitant Medication:
In the Iomeprol 300 group, 4 of 7 patients took concomitant medications. In the Iomeprol 400 group, 8 of 10 patients took concomitant medications.

Exposure to Investigational Product and/or Comparator Product:
Patient #[redacted] received the total volume of 107 mL Iomeprol 300 during the initial phase. All other patients received Iomeprol 300 (total volume 107 mL) or Iomeprol 400 (total volume 80 mL) according to the biphasic injection protocol.

Efficacy:
Analysis of efficacy was not performed.

Safety:
No adverse events, serious adverse events, or deaths were reported during this study.

Conclusions:
This randomized, double-blind, parallel-group study comparing Iomeprol 300 and Iomeprol 400 in perfusion CT in adult patients with renal carcinoma was terminated prematurely. No conclusions with regard to the primary and secondary objectives of this study can be drawn because efficacy data were neither collected nor analyzed. No adverse events occurred during the study.

Date of Report: 29 October 2010