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Name and Address of Company: Bracco ALTANA Pharma GmbH Max-Stromeyer-Str. 116 78467 Konstanz, Germany	**(For Bracco Regulatory Affairs Use Only)** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: Iomeron®	**Item #:**	
Name of Active Ingredient: Iomeprol	**Item #:**	

Title of Study:

Comparison of Iomeprol 300 and Iomeprol 400 for the Efficiency of Autosegmentation in 64-Row Multi-Detector CTA of the Coronary Arteries

Investigators/Study Center(s):

[redacted]

Publication (reference, if any): None

Study Period: First subject enrolled: 10 August 2006 Last subject completed: 6 June 2007	**Phase of Development:** IV

Objectives:

Primary:

To compare the efficiency of a body weight-adapted bolus administration of a medium concentration (Iomeprol 300) contrast agent, providing medium iodine flux, versus a high concentration (Iomeprol 400) contrast agent, providing high iodine flux, for visualization of the length of the coronary arteries in MDCTA, expressed as percentage of total automated segmentation length in relation to total manually measured segment length.

Secondary:

To compare between the medium iodine flux group (Iomeprol 300) and the high iodine flux group (Iomeprol 400):

- Length of coronary segments segmented automatically without user-interaction expressed as total;
- Number of coronary segments segmented automatically without user-interaction expressed as total and as percentage of automated in relation to manually determined segments;
- Length of coronary segments segmented semi-automatically with user-interaction expressed as total and as percentage of semi-automatically in relation to manually measured segments;
- Number of coronary segments segmented semi-automatically with user-interaction expressed as total and as percentage of semi-automatically in relation to manually determined segments, and number of interactions to manually guide a segmentation tool;
- Mean contrast density (HU) in coronary segments and left and right atrio-ventricular system.

To explore the correlation between body weight and contrast density and between body weight and visualization of coronary segments (length and number of segments).

Study Design:

Exploratory, multi-center, randomized, double-blind parallel-group comparison (2 German centers)

Patient Population:

Number of Patients Planned: 60 (30 patients per study center)
Number of Patients Enrolled: 61
Number of Patients Randomized: 61
Number of Patients Dosed: 61
Number of Patients Evaluated for Efficacy: 57
Number of Patients Evaluated for Safety: 61

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Diagnosis and Main Criteria for Inclusion:

Adult patient (age: ≥18 years; body weight: 60 to 124 kg) with suspected coronary artery occlusive disease and indication for coronary MDCTA.

Dose and Mode of Administration, Batch Number of Test Agent:

Iomeron® 300 (Iomeprol 300; batch number [redacted]) was administered by intravenous injection at a mean injection rate of 4.46 mL/s. The mean injected volume was 80.07 mL, corresponding to a body weight related iodine flux of 17.12 mg I/(s x kg). The expiry date of the investigational product was [redacted]

Dose and Mode of Administration of Comparative Agent:

Iomeron® 400 (Iomeprol 400; batch number [redacted]) was administered by intravenous injection at a mean injection rate of 4.72 mL/s. The mean injected volume was 85.45 mL, corresponding to a body weight related iodine flux of 22.96 mg I/(s x kg). The expiry date of the investigational product was [redacted]

Duration of Treatment:

This was a single dose study. The duration of the MDCTA examination was approximately 20 to 30 minutes for each patient. The safety follow-up period after the contrast agent administration was 24 hours.

Evaluation Parameters:

Efficacy:

Technical adequacy

Technical adequacy of all images/reconstructions with regard to segmentation and clinical evaluation was assessed. In case of insufficient technical quality the reason was described and the evaluation stopped.

Total length of coronary segments

The longest coronary segment (AHA 15-segment model) that was identifiable by automatic segmentation was used as the basis for the determination of the total length [mm] of this coronary segment using the following methods:

- Automatic segmentation;
- Semi-automatic segmentation;
- Manual segmentation

Total number of coronary segments

The total number of coronary segments (AHA 15-segment model) was determined using the methods listed above.

Number of interaction to manually guide the segmentation tool

For semi-automatic segmentation, the number of interactions to manually guide the segmentation tool was reported.

Contrast density measurements in the right and left ventricle and in coronary vessels

Contrast density measurements (HU) were performed along the longitudinal axis of the right and left ventricle. Regions of interest(ROI) were placed every 5 mm covering the whole left and right ventricles. An additional measurement was performed at the mitral valve plane of the left ventricle.

For the evaluation of coronary vessels, ROIs were placed in representative proximal areas of the lumen of the right coronary artery, left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, and the venous coronary sinus. Mean contrast density and standard deviation (SD) were recorded for every measurement.

Diagnosis

MDCTA images were assessed to reveal stenoses. The degree of the largest stenosis was determined (<50%, ≥50% to <75%, ≥75% to <100%, or 100% of lumen diameter). The location of the stenoses and any other relevant diagnostic information were reported.

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Evaluation Parameters (continued):

Safety

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

Statistical Methods:

Demographics and Baseline Characteristics:

Summary tables were provided for the number of subjects who had been screened, randomized, dosed and completed the study according to the protocol guidelines. Likewise, summary tables were provided for demographic and baseline characteristics including age, sex, ethnic origin, height, and weight. Frequency distribution tables (N, %) were produced for categorical data and summary statistics (n, mean, SD, Q1, median, Q3, minimum, maximum) for continuous data.

Efficacy:

*Primary **Efficacy Analysis***

The primary efficacy variable was the percentage of total automated segmentation length in relation to total manually measured segment length:

$$\%SL = (TSL_{\text{automated segmentation}}) \times 100 / TSL_{\text{manual segmentation}}$$

Where: %SL = Percentage of segment length
TSL = Total length of segments determined [mm]

The percentage of total automated segmentation length was compared between study groups by means of a WILCOXON MANN-WHITNEY U test.

Secondary Efficacy Analyses

For the secondary efficacy variables, summary statistics (n, mean, SD, Q1, median, Q3, minimum, maximum) were produced. WILCOXON MANN-WHITNEY U tests were applied to compare the study groups.

- Total automated segment length [mm];
- Total number of automated segments;
- Percentage of automated segments in relation to manually determined segments;
- Total semi-automated segment length [mm];
- Percentage of semi-automated segment length [mm] in relation to manually determined segment length [mm];
- Total number of semi-automated segments;
- Percentage of semi-automated segments in relation to manually determined segments;
- Number of interaction in semi-automated segmentation to manually guide the segmentation tool;
- Average contrast density [HU] of the right ventricle;
- Average contrast density [HU] of the left ventricle;
- Contrast density [HU] of coronary vessels;
- Average contrast density [HU] over all coronary vessels.

For automatic and semi-automated segmentation, the percentage of total number of segments in relation to total manually determined segments were calculated and analyzed:

$$\%SN = (TSN_{\text{semi-/automated segmentation}}) \times 100 / TSN_{\text{manual segmentation}}$$

Where: %SN = Percentage of number of segments
TSN = Total number of segments determined

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Statistical Methods (continued):

Secondary Efficacy Analyses (continued)

Contrast density:

The individual average of all measurements of the right ventricle, the individual average of all measurements of the left ventricle, and the individual average of all coronary artery measurements were calculated and analyzed. Contrast densities were also analyzed by coronary vessels.

Further analyses:

Scatter plots were produced displaying contrast densities vs. body weight, and length and numbers of automated segments vs. body weight. Correlation analyses were performed.

Safety:

Safety analysis was performed on the Safety Population (SAF) and based on the analysis of adverse events. Only postdose untoward medical events occurring up to 24 hours after administration of investigational product were classified as adverse events. Adverse events were summarized by COSTART body system, MedDRA preferred term, and by intensity and causal relationship to the investigational product.

Results and Conclusions:

There were 61 patients enrolled, randomized and dosed in this study, 30 patients in the Iomeprol 300 arm and 31 in the Iomeprol 400 arm. The safety population consisted of all patients. There were 4 patients less in the efficacy population due to missing data, technical inadequacy and inappropriate dosage of the investigational product.

Demographics:

Overall, demographic data were comparable between the Iomeprol 300 and Iomeprol 400 groups. Slightly more men than women were included in both groups. In the SAF, men represented 56.7% of patients in the Iomeprol 300 group and 58.1% in the Iomeprol 400 group. The mean age and weight were slightly but not statistically significantly higher in the Iomeprol 400 group than in the Iomeprol 300 group. In the SAF, the mean age was 57.0 ± 12.5 years in the Iomeprol 300 group and 62.1 ± 9.2 years in the Iomeprol 400 group. The mean weight was 78.1 ± 13.1 kg and 82.4 ± 16.1 kg, respectively, in the 2 study groups. Except for 1 Eurasian patient in each study group, all participants were white.

Exposure to Investigational Product and/or Comparator Product:

In the Iomeprol 300 group (SAF), the mean administered volume was 80.07 ± 14.09 mL at a mean injection rate of 4.46 ± 0.78 mL/s and the mean body weight related iodine flux was 17.12 ± 0.43 mg I/(s x kg). In the Iomeprol 400 group (SAF), the mean administered volume was 85.45 ± 16.74 mL at a mean injection rate of 4.72 ± 0.87 mL/s and the mean body weight related iodine flux was 22.96 ± 0.78 mg I/(s x kg).

In the EFF, there was a slight difference only in the mean administered volume in the Iomeprol 400 group (84.18 ± 16.35 mL).

Efficacy:

Primary Endpoint

Segmentation

There was no statistically significant difference between the Iomeprol 300 and the Iomeprol 400 groups with regard to the percentage of total automated segment length vs. manually measured segment length. Although the mean value was numerically higher in the Iomeprol 400 group (67.7 ± 18.2%) than in the Iomeprol 300 group (62.8 ± 21.0%), the Wilcoxon Mann Whitney U test yielded no statistically significant difference between the groups (p=0.4677).

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Results and Conclusions (continued):

Efficacy (continued):

Secondary Endpoints

Segmentation

Overall, the measured mean total segment lengths were numerically higher with Iomeprol 400 than with Iomeprol 300, irrespective of the segmentation method used. The differences between the treatment groups were not statistically significant. The mean total segment length determined by automatic segmentation was 254.8 ± 105.8 mm with Iomeprol 300 and 295.8 ± 110.9 mm with Iomeprol 400 (p=0.2504, Wilcoxon Mann Whitney U test). The mean total segment length determined by semi-automatic segmentation was 391.6 ± 75.2 mm with Iomeprol 300 and 417.4 ± 76.2 mm with Iomeprol 400 (p=0.2312, Wilcoxon Mann Whitney U test). The manually determined mean total segment length was 398.6 ± 64.5 mm with Iomeprol 300 and 427.4 ± 67.4 mm with Iomeprol 400 (p=0.1104, Wilcoxon Mann Whitney U test).

There was no statistically significant difference between the groups regarding the mean percentage of total semi-automated segment length vs. manually measured segment length (Iomeprol 300: 98.2 ± 9.3%, Iomeprol 400: 97.5 ± 6.5%; p=0.0784, Wilcoxon Mann Whitney U test).

The mean total numbers of segments that were identified by automatic, semi-automatic, or manual segmentation were higher with Iomeprol 400 than with Iomeprol 300. Statistical significance for the between-group difference was reached only with automatic segmentation. The mean total number of segments identified by automatic segmentation was 9.2 ± 3.5 with Iomeprol 300 and 11.1 ± 2.9 with Iomeprol 400. The between-group difference was statistically significant (p=0.0467, Wilcoxon Mann Whitney U test). The mean total number of semi-automatic segments was 13.7 ± 1.4 with Iomeprol 300 and 14.0 ± 1.2 with Iomeprol 400 (p=0.2894, Wilcoxon Mann Whitney U test). The mean total number of manually determined segments was 13.8 ± 1.2 with Iomeprol 300 and 14.1 ± 1.0 with Iomeprol 400.

No statistically significant between-group differences was observed for the percentage of automated vs. manually determined number of segments (Iomeprol 300: 66.6 ± 23.8%, Iomeprol 400: 77.5± 16.7%; p=0.0720, Wilcoxon Mann Whitney U test) or the percentage of semi-automated vs. manually determined number of segments (Iomeprol 300: 99.0 ± 4.4%, Iomeprol 400: 99.2 ± 2.4%; p=0.6371, Wilcoxon Mann Whitney U test).

The mean number of interactions to manually guide the segmentation tool during semi-automated segmentation was 9.9 with Iomeprol 300 and 8.3 with Iomeprol 400 (p=0.4659, Wilcoxon Mann Whitney U test).

Contrast Densities

The between-group comparisons of the mean average contrast densities in the right ventricle, the left ventricle, and all coronary vessels revealed statistically significant differences in favor of the higher contrast agent concentration (Iomeprol 400). The mean average contrast density in the right ventricle was 184.9 ± 87.6 HU with Iomeprol 300 and 238.4 ± 91.0 HU with Iomeprol 400 (p=0.0186, Wilcoxon Mann Whitney U test). In the left ventricle, the mean average contrast densities were 291.6 ± 46.3 HU with Iomeprol 300 and 376.9 ± 65.8 HU with Iomeprol 400 (p<0.0001, Wilcoxon Mann Whitney U test). In the coronary vessels, the mean average contrast density was 259.4 ± 39.6 HU in the Iomeprol 300 group and 327.0 ± 54.6 HU in the Iomeprol 400 group (p<0.0001, Wilcoxon Mann Whitney U test).

The mean contrast densities measured in the single coronary arteries were statistically significantly higher with Iomeprol 400 than with Iomeprol 300 (p<0.05, Wilcoxon Mann Whitney U test). The highest contrast densities were measured in the left main coronary artery: 309.0 ± 49.1 HU with Iomeprol 300 and 390.3 ± 63.6 HU with Iomeprol 400 (p<0.0001, Wilcoxon Mann Whitney U test).

Diagnosis

The majority of patients, 51.7% in the Iomeprol 300 group and 71.4% in the Iomeprol 400 group had no stenoses, i.e., normal segments. Stenoses of <50% lumen diameter were diagnosed in more than 20% of patients in both groups. One occlusion was reported for 1 patient in the Iomeprol 300 group.

Correlation Analyses

There were no relevant correlations between body weight and segment length, body weight and total number of segments, or body weight and contrast density (left ventricle, right ventricle, or coronary vessels).

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Summary and Conclusions (continued):

Safety:

In total, 2 patients experienced adverse events in this study, i.e., 1 patient in each study group experienced 1 adverse event each. The adverse event 'urticaria' reported by the patient in the Iomeprol 300 group was classified as an adverse event due to local site reaction and was assessed by the Investigator as probably related to the investigational product. The intensity of the adverse event was mild and resolved after approximately 3 hours. The adverse event 'extrasystole' reported by the patient in the Iomeprol 400 group was of moderate intensity and was assessed by the Investigator as not related to the investigational product. The patient recovered within a few minutes.

No patient discontinued the study due to an adverse event. No serious adverse events or deaths were reported during this study.

Conclusions:

The following conclusions can be drawn from this exploratory, randomized, double-blind, parallel-group study, comparing Iomeprol 300 and Iomeprol 400 in MDCTA of coronary arteries:

- There was no difference in visualization of coronary artery lengths in MDCTA between the Iomeprol 300 and Iomeprol 400 groups.
- There was no difference in the numbers of visualized coronary segments in semi-automatic and manual modes between the 2 treatment groups. The number of visualized coronary segments in the automatic mode was higher in the Iomeprol 400 group than in the Iomeprol 300 group.
- There were no differences in the total length of visualized coronary segments between the 2 treatment groups.
- There were no differences in the numbers of manual interactions required to guide the segmentation tool in the semi-automatic mode between the 2 treatment groups.
- Contrast density measurements showed a clear advantage for Iomeprol 400 when compared with Iomeprol 300.
- Two adverse events occurred in 2 patients during the study. Only 1 of the adverse events (urticaria) was considered as probably related to the administered investigational product. The reaction was mild and resolved within a few hours.

Overall, with regard to the quantitative assessments of coronary segments in MDCTA, the present study revealed numerically but not statistically significantly higher mean values for the high iodine flux group (Iomeprol 400) than the medium iodine flux group (Iomeprol 300). However, the results did show a consistent trend in favor of Iomeprol 400. Furthermore, Iomeprol 400 yielded significantly higher average contrast densities than Iomeprol 300 in both ventricles and the coronary vessels. The good safety profile of Iomeprol was confirmed.

Date of Report: 17 March 2008