2 Synopsis

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:
A Double-Blind Inter-Individual Comparison of Iomeprol 300 and Iomeprol 400 in Multi-Detector CT Angiography (MDCTA) of Peripheral Arteries.

Investigators/Study Center(s):
[redacted]

Publication (reference, if any): None

Study Period: First subject enrolled: 30 March 2006 Last subject completed: 25 May 2007	**Phase of Development:** IV

Objectives:
Primary:

To quantitatively compare the vascular opacification in terms of contrast density (HU) in MDCTA of peripheral arteries between a long bolus injection of Iomeprol 300 and a short bolus injection of Iomeprol 400 at equal iodine amounts.

Secondary:
To compare between the Iomeprol 300 and Iomeprol 400 injection protocols:

- Contrast density (HU) in certain arterial and venous vessel segments;
- Qualitative evaluations of vascular opacification;
- Overriding of contrast bolus;
- Venous overlap.

Study Design:
Multicenter, randomized, double-blind parallel-group comparison (2 German centers)

Subject Population:
Number of Subjects Planned: 64 (32 patients per study center)
Number of Subjects Enrolled: 69
Number of Subjects Randomized: 69
Number of Subjects Dosed: 69 (Iomeprol 300: 34 patients; Iomeprol 400: 35 patients)
Number of Subjects Evaluated for Efficacy: 64
Number of Subjects Evaluated for Safety: 69

Diagnosis and Main Criteria for Inclusion:
Adult patient (age: ≥18 years) with suspected peripheral artery occlusive disease and indication for MDCTA

Dose and Mode of Administration, Batch Number of Test Agent:
A total of 134 mL of Iomeron® 300 (Iomeprol 300; batch number [redacted]) was administered by intravenous injection at an injection rate of 4.0 mL/s, corresponding to an injection duration of 33.5 seconds and a flux of 1.2 g iodine per second. The total iodine amount was 40 g. The expiry date of the investigational product was [redacted].

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Dose and Mode of Administration of Comparative Agent:
A total of 100 mL of Iomeron® 400 (Iomeprol 400; batch number [redacted]) was administered by intravenous injection at an injection rate of 4.0 mL/s, corresponding to an injection duration of 25 seconds and a flux of 1.6 g iodine per second. The total iodine amount was 40 g. 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 15 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 efficacy analysis was assessed. In case of insufficient technical quality due to reasons other than related to the timing of the contrast bolus, the reason was described and the evaluation stopped.

Quantitative Assessments
Vascular contrast density (HU) was measured intravascular using regions of interest as large as appropriate within the lumen of the following vessel segments (axial images):

- Abdominal aorta (approximately 2 cm above renal arteries);
- Distal aorta and inferior vena cava (approximately 5 cm above aortic bifurcation);
- External iliac arteries right and left (approximately 2 cm below the iliac bifurcation);
- Superficial femoral arteries and veins right and left (approximately 2 cm below the femoral bifurcation);
- Superficial femoral arteries right and left (approximately 15 cm below the femoral bifurcation);
- Popliteal arteries and veins right and left (at the level of the distal intercondylar region of the femur);
- Anterior tibial arteries and tibioperoneal trunk right and left (at the level of the middle of the trunk);
- Anterior and posterior tibial arteries, as well as peroneal arteries right and left (approximately 15 cm below the bifurcations of the tibioperoneal trunk);
- Anterior and posterior tibial arteries and veins, as well as peroneal arteries and veins right and left (approximately 2 cm above the level of the ankle joint);
- Dorsalis pedis and plantar arteries, right and left (at the metatarsal level).

Anatomical regions where the vascular opacification was not measurable due to underlying arterial occlusions or other reasons (small vessel diameter) had to be indicated.
If present, contrast density in the superficial venous system was also measured in the greater saphenous vein or any other visible superficial vein at the following levels:

- Orifice of the greater saphenous vein;
- Knee joint;
- Ankle joint.

In the case of presence of more than one enhanced vein at a specific level, the vein with the highest opacification was used for contrast density measurement.

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Evaluation Parameters (continued):

Efficacy (continued):

Qualitative Assessments

Axial images, and coronal or para-coronal (pelvis) maximum intensity projection (MIP) images (thickness 10 mm; increment 3 mm) were used for qualitative assessments.

Vascular opacification

The quality of vascular opacification was assessed in view of detection/exclusion of vascular lesions separately for the following segments:

- Pelvic arteries, up to the inguinal ligament;
- Femoropoliteal segment, up to the end of the popliteal artery;
- Lower leg, up to the ankle;
- Feet.

The following scores were applied:

1 = Poor:	Little to no opacification of the arteries, preventing any visualization of vascular margins, plaques, aneurysms, thrombi or occlusions.
2 = Insufficient:	Some, but incomplete opacification of arteries. Adequate diagnosis of plaques, thrombi or occlusions of those arteries is still not possible.
3 = Fair:	Opacification of the arteries versus adjacent soft tissue allows a barely adequate visualization of margins, plaques, aneurysms, thrombi and occlusions of those arteries. Diagnostic procedures are time consuming.
4 = Good:	Opacification of the arteries versus adjacent soft tissue allows good and almost full though perhaps not rapid and easy visualization of margins, plaques, aneurysms, thrombi and occlusions. Some minor parts of the opacification may still not be complete or homogenous.
5 = Excellent:	Complete opacification, with full demonstration of intra-luminal anatomy, down to branch arteries and expected collaterals, enables a rapid and easy diagnosis of plaques, aneurysms, thrombi and occlusions of those arteries.

The quality of contrast opacification in the so-appearing collateral vessels in the case of arterial stenoses were assessed separately in the same way.

Overriding of the contrast bolus

The presence of an overriding of the contrast bolus (resulting in an unacceptable low opacification of the peripheral arteries) were described as follows:

1 = No:	May include a reduction of contrast density at the periphery, but without diagnostic impact;
2 = Low:	Insufficient vascular opacification preventing a sufficient diagnosis at the foot level;
3 = Considerable:	Insufficient vascular opacification preventing a sufficient diagnosis from the lower leg level on;
4 = Predominant:	Insufficient vascular opacification preventing a sufficient diagnosis from the thigh level on;
5 = Non diagnostic:	Insufficient vascular opacification preventing a sufficient diagnosis from the pelvic level on.

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Evaluation Parameters (continued):

Efficacy (continued):

Venous overlap

The presence of a venous overlap, either superficially or deeply, was assessed separately for the following anatomical levels:

1 = No No venous overlap;
2 = ankle Venous overlap present at the ankle level;
3 = knee Venous overlap present at the knee level;
4 = inguinal Venous overlap present at inguinal level.

If a venous overlap was present, it was stated whether or not it interfered with diagnosis.
Assessments of the vascular opacification, the bolus overriding, and the venous overlap were done separately for each lower extremity. Any assumable anatomical/pathological reasons (aneurysms, stenoses, ulcerations) were described briefly.

Diagnosis

Diagnosis was given separately for each of the following arterial segments at both legs:

- Abdomen: Abdominal aorta and major branches;
- Pelvis; up to the inguinal ligament;
- Thigh; up to the end of the popliteal artery;
- Lower leg; up to the ankle joint;
- Feet.

Arterial segments were assessed according to the following scale:
1 = Normal;
2 = Stenosis <50%;
3 = Stenosis ≥50% and <75%;
4 = Stenosis ≥75% and <100%;
5 = Occlusion;
6 = Unclear.

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 patients who had been screened, dosed and completed the study according to the protocol guidelines. Summary tables were provided for demographic and baseline characteristics, including age, height, weight, sex, and ethnic origin. Descriptive statistics (N, mean, standard deviation [SD], Q1, median, Q3, minimum, maximum) were performed for continuous data. Frequency distributions (N, percentage) were calculated for categorical data.

Efficacy:

The analysis of efficacy was based on the Efficacy Population (EFF).
The between-group difference in the individual average of contrast density measurements (primary efficacy endpoint) was tested by an unpaired t-test. All other statistical tests were considered exploratory. No adjustment for multiplicity was therefore carried out. All statistical tests were performed with a two-sided alpha level of 5%.

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Statistical Methods (continued):
Efficacy (continued):

Primary Efficacy Analysis
The primary efficacy variable was the individual average of all contrast density measurements (HU) of arterial segments.
H_0-hypothesis: There is no difference between Iomeprol 300 and Iomeprol 400 injection protocols in the contrast density of peripheral arteries.
The hypothesis was tested by an unpaired t-test. Null hypothesis was to be rejected with $p < 0.05$.

Secondary Efficacy Analyses
Comparison between Iomeprol 300 and Iomeprol 400:

- Contrast density (each segment);
- Vascular opacification;
- Overriding of contrast bolus;
- Venous overlap.

Further Information: diagnosis (stenosis score)

In general, categorical data was presented by frequency distribution tables by study groups and anatomical areas, continuous data by summary statistics (N, mean, SD, Q1, median, Q3, minimum, maximum) by study groups and anatomical areas.

Arterial Opacification:
Arterial opacification was analyzed by segments and overall, by calculating the individual average of assessment scores. A WILCOXON MANN-WHITNEY U test was applied to compare the individual averages between study groups.
Contrast density:
Contrast density (HU) was reported separately for each segment and side (right/left). Differences between study groups were explored using unpaired t-tests.
Correlation Analyses:
The individual averages of all arterial segments were plotted against the body weight of patients, separately for each study group. Regression analyses were performed to describe the correlation between body weight and contrast density mathematically.

Safety:
Safety data were summarized for all patients dosed with the investigational product (Safety Population [SAF]). Safety analysis was based on the analysis of adverse events.
Adverse events were summarized by COSTART body system and preferred term, by intensity, and by causal relationship to investigational product for all patients in the SAF. Concomitant medication data was presented in data listings.

Summary and Conclusions:

Demographics:
Overall, demographic data were comparable between the Iomeprol 300 and Iomeprol 400 groups. In the Iomeprol 400 group, more men were included than women (68.6% vs. 31.4% of patients in the SAF). The proportion of male and female patients was more balanced in the Iomeprol 300 group (52.9% vs. 47.1% in the SAF). The mean age in the SAF population was slightly higher in the Iomeprol 400 group (68.7 years) than in the Iomeprol 300 group (64.7 years). With regard to weight and height, there were no differences between the study groups. The mean weight of SAF-patients was 77.6 ± 11.6 kg in the Iomeprol 300 group and 77.9 ± 12.0 kg in the Iomeprol 400 group. SAF patients had a mean height of 171.6 ± 7.7 cm in both study groups. All patients who participated in the study were white.

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Summary and Conclusions (continued):

Exposure to Investigational Product and/or Comparator Product:

All 34 patients in the Iomeprol 300 group received the planned volume of 134 mL contrast agent at an injection rate of 4 mL/s, corresponding to a flux of 1.2 g iodine per second. In the Iomeprol 400 group, 34 patients received the planned volume of 100 mL contrast agent at an injection rate of 4 mL/s, corresponding to a flux of 1.6 g iodine per second. The total iodine amount was 40 g in both study groups. Due to technical problems, 1 patient received an initial volume of 27 mL Iomeprol 400 and after 27 minutes an additional volume of 100 mL Iomeprol 400. This protocol violation was considered minor and the patient was not excluded from the efficacy analysis.

Efficacy:

Primary Endpoint

The individual average over all arterial contrast density measurements was higher in the Iomeprol 400 group (278.6 ± 57.4 HU) than in the Iomeprol 300 group (233.9 ± 31.8 HU). The difference was statistically significant (p=0.0017, unpaired t-test).

Secondary Endpoints

Contrast Densities in Arterial Segments

Overall, all mean values of the contrast densities in the arterial segments were numerically higher in the Iomeprol 400 group than in the Iomeprol 300 group. Statistically significant differences ($p<0.05$, unpaired t-test) were observed in the abdominal aorta (282.8 vs. 348.9 HU), the distal aorta (279.2 vs. 362.1 HU), the external iliac arteries (both sides: 263.5 vs. 350.9 HU), the superficial femoral arteries (2 cm below bifurcation, both sides: 275.6 vs. 342.9 HU), the popliteal arteries (both sides: 318.7 vs. 375.7 HU), and the peroneal arteries (15 cm below bifurcation, both sides: 198.1 vs. 243.1 HU; 2 cm above ankle joint, both sides: 118.5 vs. 160.0 HU). In both groups, the highest mean values were reached in the popliteal arteries and the lowest mean values were obtained in the peroneal arteries 2 cm above the ankle joint.

Qualitative Assessment of Arterial Opacification

The qualitative assessment of arterial opacification resulted in a higher number of patients with complete opacification (score = 5 'excellent') in all right and left arterial segments (pelvic, femoropopliteal, lower leg, and feet) in the Iomeprol 400 group (72.3% of all assessed segments) than in the Iomeprol 300 group (59.0% of all assessed segments). However, the comparison of the mean score values calculated from the individual means of all arterial segments (Iomeprol 300: 4.40, Iomeprol 400: 4.52) revealed no statistically significant difference between the groups (p=0.1012, Wilcoxon Mann Whitney U test). A similar result was obtained for the mean score values of the individual arterial segments ($p\geq0.1701$, Wilcoxon Mann Whitney U test).

Overriding of Contrast Bolus

Insufficient opacification due to overriding of contrast bolus was observed in only a few patients. There was no relevant difference in the frequency of bolus overriding between the long bolus injection of Iomeprol 300 and the short bolus injection of Iomeprol 400. No overriding of contrast bolus in the right body side was observed in 31 patients (96.9%) in the Iomeprol 300 group and 30 patients (93.8%) in the Iomeprol 400 group, respectively. Likewise, for the same number of patients in each group, no overriding of contrast bolus was observed in the left body side. One patient in the Iomeprol 300 group had considerable bolus overriding affecting the right and the left body sides with inefficient vascular opacification from the right lower leg level on. Bolus overriding was observed in a total of 3 patients in the Iomeprol 400 group: 1 patient had considerable bolus overriding in both body sides, 1 patient had considerable bolus overriding in the right body side and 1 patient had low bolus overriding affecting the left body side. Anatomical/pathological reasons for the contrast bolus overriding were assumed for the 2 patients with considerable bolus overriding in the Iomeprol 400 group. No anatomical/pathological reasons were found for the affected patient in the Iomeprol 300 group.

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Summary and Conclusions (continued):

Efficacy (continued):

Secondary Endpoints (continued)

Contrast Densities in Venous Segments

Overall, mean contrast densities in individual deep venous segments of the abdomen, upper leg, and lower leg were low, i.e., between 45.7 HU (inferior vena cava) and 80.4 HU (peroneal veins), without any relevant differences between the injection protocols. Although numerically not large, the only exception was the differences in the inferior vena cava with mean values of 50.9 HU in the Iomeprol 300 group and 45.7 HU in the Iomeprol 400 group (p=0.0239, unpaired t-test). The mean values of the individual average over all venous contrast density measurements were 58.0 HU (Iomeprol 300) and 55.5 HU (Iomeprol 400). No statistically significant difference was observed in the between-group comparison (p=0.2919, unpaired t-test).

Similar to the deep venous segments, the contrast densities in the superficial venous system were low in the upper legs and knees (orifice of the greater saphenous vein, knee joints). Higher contrast densities were only measured in the right and left ankle joints with mean values of 125.3 and 116.3 HU in the Iomeprol 300 group, and 110.8 and 115.5 HU in the Iomeprol 400 group. There were no statistically significant between-group differences.

Venous Overlap

Venous overlaps were less frequently observed in the Iomeprol 400 group than the Iomeprol 300 group. In the Iomeprol 300 group, 13 out of 32 patients (40.6%) had no overlap at all, compared with 20 out of 32 patients (62.5%) in the Iomeprol 400 group. The majority of venous overlaps occurred at ankle level. Affected were 40.6% (right side) and 37.5% (left side) of patients in the Iomeprol 300 group, and 28.1% (right side) and 15.6% (left side) of patients in the Iomeprol 400 group. Overlaps were observed in 9.4% (knee level, both sides, respectively), in 3.1% (inguinal level, left side), and in 3.1% and 6.3% (ankle + knee level, right and left) of patients in the Iomeprol 300 group. In the Iomeprol 400 group, venous overlaps occurred in 3.1% and 9.4% (knee level, right and left), in 0% (inguinal level), and in 3.1% (ankle + knee level, both sides, respectively) of patients. In the Iomeprol 300 group, overlaps were more often superficially than deep, whereas there was no clear trend in the Iomeprol 400 group.

In both groups, venous overlap did not interfere with diagnosis in any of the affected patients.

Anatomical/pathological reasons for venous overlaps were assumed for 2 out of the 12 affected patients in the Iomeprol 400 group, but for none of the 19 patients in the Iomeprol 300 group.

Diagnosis

The diagnosis of stenoses in arterial segments revealed only a slight difference between the study groups in the frequency of pathological findings. Out of 352 assessed segments per group, 146 were rated as normal in the Iomeprol 300 group and 137 in the Iomeprol 400 group. A slightly higher number of stenoses of more than 50% and less than 75% of lumen diameter were found in the Iomeprol 400 group (24) group than in the Iomeprol 300 group (14). Between the Iomeprol 300 and Iomeprol 400 groups, the number of stenoses of less than 50% (76 vs. 73), of more than 75% but less than 100% (21 vs. 20), and occlusions (91 vs. 92) was comparable.

The abdominal aorta segment was most frequently rated as normal, whereas the right and left lower legs were least frequently assessed as normal in both groups. In the right and left thigh, obstructive stenoses (>50% of lumen diameter) were less frequent in the Iomeprol 300 group (50% both sides) than in the Iomeprol 400 group (62.5%, 71.9%). In the right and left foot, obstructive stenoses were more frequent in the Iomeprol 300 group (59.4%, 56.3%) than the Iomeprol 400 group (43.8%, both feet).

Correlation Analyses

In the Iomeprol 400 group, a very weak correlation was found between arterial contrast density and body weight, i.e., contrast densities decreased with increasing body weight (correlation coefficient: -0.5136). A similar, but even weaker trend was found in the Iomeprol 300 group (correlation coefficient: -0.2436).

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Summary and Conclusions (continued):

Safety:
No adverse events, serious adverse events, or deaths occurred during this study.
No patient discontinued the study due to an adverse event.

Conclusions:

The following conclusions can be drawn from this randomized, double-blind, parallel-group study, comparing a long bolus administration of Iomeprol 300 and a short bolus administration of Iomeprol 400 in MDCTA of peripheral arteries:

- The primary efficacy variable, i.e., the individual average over all arterial contrast density measurements was statistically significantly higher in the Iomeprol 400 group than in the Iomeprol 300 group (278.6 vs. 233.9 HU; p=0.0017, unpaired t-test).
- The mean contrast densities in all analyzed individual arterial segments were higher in the Iomeprol 400 group than in the Iomeprol 300 group. Statistical significance ($p \leq 0.0314$, unpaired t-test) was reached in several segments, down to the level of the peroneal arteries (15 cm below bifurcation and 2 cm above ankle joint).
- The qualitative assessment of arterial opacification revealed numerically, but not significantly ($p \geq 0.1012$, Wilcoxon Mann Whitney U test), higher mean score values in the Iomeprol 400 group. The mean score values of the individual average over all arterial segments were 4.40 (Iomeprol 300) and 4.52 (Iomeprol 400).
- Insufficient opacification due to bolus overriding was rare and there was no relevant difference between the injection protocols.
- The mean contrast densities in the deep venous segments were generally low, and in many analyzed segments mean values were numerically lower with Iomeprol 400 than with Iomeprol 300. However, the difference between the mean values of the individual average over all venous contrast density measurements was not statistically significant (p=0.2919, unpaired t-test). Likewise, the contrast densities in the superficial venous system were low in the upper legs and knees. Higher contrast densities of more than 100 HU were only measured in the right and left ankle joints. There were no relevant between-group differences in contrast densities in the superficial venous system.
- Venous overlaps were less frequently observed in the Iomeprol 400 group than the Iomeprol 300 group. The highest number of overlaps occurred at ankle level (right and left sides) in both groups (Iomeprol 300: 40.6%, 37.5%; Iomeprol 400: 28.1%, 15.6%). Venous overlap did not interfere with diagnosis in any of the patients.
- No adverse events occurred during this study.

Overall, the results of the present study showed an advantage of the short bolus administration of Iomeprol 400 versus the long bolus administration of Iomeprol 300 at equal iodine amounts. This was most evident in the statistically significantly higher mean contrast density calculated from all arterial measurements. Furthermore, fewer cases of venous contamination were found in the Iomeprol 400 group, without increased risk of bolus overriding in peripheral MDCTA.

The good safety profile of Iomeprol was confirmed.

Date of Report: 10 April 2008