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Name and Address of Company: Bracco Imaging Deutschland 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:
PET/CT with Iomeron® 400 in Patients with Suspected Malignant Liver Lesions – A Feasibility Study

Investigators/Study Center(s):
[redacted]

Publication (reference, if any): None

Study Period: First subject enrolled: 25 October 2006 Last subject completed: 10 July 2008 Off-site assessment: Not applicable	**Phase of Development:** IV

Objectives:
Objectives of the present study were:

- To explore the influence of Iomeprol 400 on positron emission tomography (PET) of the liver by:
  - Comparing Standard Uptake Values (SUV) of liver lesions and normal liver tissue between precontrast-CT corrected, arterial-phase-CT corrected, portal-venous-phase-CT corrected, and late-phase CT corrected PET maps,
  - Comparing qualitative assessments obtained on the basis of PET maps which were corrected with precontrast CT, arterial-phase CT, portal-venous-phase CT, and late-phase CT; and
- To show the usefulness of Iomeprol 400 in multidetector computed tomography (CT) of the liver by:
  - Comparing contrast density measurements (Hounsfield Unit) of liver lesions and normal liver tissue between precontrast CT, arterial-phase CT, portal-venous-phase CT and late phase CT,
  - Comparing qualitative assessments between images of precontrast CT, arterial-phase CT, portal-venous-phase CT and late phase CT.

Study Design:
Phase IV, single-center, open-label, exploratory trial. Imaging methods were compared intra-individually.

Subject Population:
Number of Subjects Planned: 20 (with PET positive lesions)
Number of Subjects Enrolled: 28
Number of Subjects Randomized: not applicable
Number of Subjects Dosed: 28
Number of Subjects Evaluated for Efficacy: 28 (21 with PET positive lesions)
Number of Subjects Evaluated for Safety: 28

Diagnosis and Main Criteria for Inclusion:
Adult patient (age: ≥18 years) with highly suspected or proven malignant liver lesions and given indication for PET and CT.

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Dose and Mode of Administration, Batch Number of Test Agent:
100 mL Iomeron® 400 (Iomeprol 400; batch number [redacted]) were administered intravenously into the left cubital vein by means of a power injector using a biphasic injection protocol with the first 70 mL injected at a flow of 2.5 mL/s and the remaining 30 mL injected at a flow of 2.1 mL/s. Contrast agent injection was immediately followed by a 40 mL flush of physiological saline (0.9% NaCl solution) injected at a flow of 2.1 mL/s. Bolus tracking technique was applied to trigger the start of CT scans. The expiry date of the investigational product was [redacted]

Dose and Mode of Administration of Comparative Agent:
Not applicable.

Duration of Treatment:
This was a single-dose study. The duration of the examination was approximately 120 minutes from administration of F-18 FDG to the end of the PET scan. The safety follow-up period after the contrast agent administration was 24 hours.

Evaluation Parameters:
Efficacy

PET Maps

UNPAIRED ASSESSMENTS

The following assessments were performed separately for the following attenuation corrected PET map sets strictly in the following sequence:

1. Arterial-phase CT correction;
2. Portal-venous-phase CT correction;
3. Late-phase CT correction;
4. Precontrast CT correction.

Technical adequacy
It was stated whether the PET maps were technically adequate to allow the performance of efficacy assessments. If the images were not technically adequate, the assessment of the respective image set had to be stopped and reasons had to be described.

Lesion detection
The number of liver lesions detected, smallest, and largest metabolic tumor volume (MTV) were reported. Up to 10 of the largest lesions were drawn on liver maps, and were numbered. The 5 largest lesions were described in more detail: localization (liver segment), MTV and characterization (malignant/indeterminate/benign) were given.

Quality of contrast and delineation
The quality of contrast and delineation of lesions will be assessed using the following 4-point scale:

1 = Insufficient
2 = Fair
3 = Good
4 = Excellent

Quantitative assessments: SUV measurements
SUVs (mean and maximum) were measured for the largest lesion of a patient, for 3 largest liver lesions, and surrounding normal tissue.

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Evaluation Parameters (continued):

Efficacy (continued)

PAIRED ASSESSMENTS

In matched pair assessments, the following 3 pairs of attenuation corrected PET map sets were directly compared:

- Precontrast correction vs. arterial phase correction;
- Precontrast correction vs. portal-venous phase correction;
- Precontrast correction vs. late phase correction.

Artifacts

The presence of artifacts related to the CT correction, and the potential influence on the detectability and delineability of liver lesions were assessed by comparing arterial, portal-venous, and late phase correction vs. the precontrast phase correction using the following 5-point scale:

1 = No artifacts
2 = Minor artifacts
3 = Moderate artifacts, but diagnostic
4 = Substantial artifacts, still partly diagnostic
5 = Substantial artifacts, non-diagnostic

Image quality

If lesions were present, the image quality of the precontrast correction PET map (Exam 1) was compared with a postcontrast correction PET map (Exam 2, separately for each phase) with regard to the ability to detect and delineate liver lesions, using the following 7-point scale:

-3 = Exam 1 is substantially better
-2 = Exam 1 is moderately better
-1 = Exam 1 is minimally better
0 = Exams are equal
1 = Exam 2 is minimally better
2 = Exam 2 is moderately better
3 = Exam 2 is substantially better

Change in diagnosis

In case the image quality of 2 PET maps compared was not equal (score was different from "0"), the Investigator stated whether or not the superiority of 1 of the 2 Exams would have changed the diagnosis. If so, the additional information leading to a change in diagnosis was described briefly.

CT Images

The following qualitative assessments were performed for the combination of all pre- and postcontrast image sets.

Technical adequacy

It was stated whether the CT image sets were technically adequate to allow the efficacy assessments. If the images were not technically adequate, the assessment of the respective image set had to be stopped and reasons had to be described.

Lesion detection

The number of liver lesions ≥ 1 cm, smallest, and largest size were reported. Up to 10 of the largest lesions > 1 cm were drawn on liver maps, and were numbered. The 5 largest lesions were described in more detail: localization (liver segment), size (mm), characterization (malignant/indeterminate/benign), and diagnosis were given.

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Evaluation Parameters (continued):

Efficacy (continued)

Image quality

Image quality with regard to the detectability, delineability and characterization of lesions of the liver was assessed using the following 5-point scale:

1 = Poor
2 = Insufficient
3 = Fair
4 = Good
5 = Excellent

Quantitative assessments: HU measurements

Contrast densities (HU) were measured in the solid tumor tissue for the 3 largest liver lesions and corresponding surrounding normal tissue separately for each CT imaging modality. Region of interest size was adjusted to the largest possible solid tumor tissue.

Combined PET/CT Assessment

The combined PET/CT assessment was performed after all separate assessments of imaging modalities. Fused PET/CT images were used for this assessment.

Lesion detection

The number of liver lesions ≥ 1cm, smallest, and largest size were reported. Up to 10 of the largest lesions were drawn on liver maps, and will be numbered. The 5 largest lesions were described in more detail: localization (liver segment), size (mm), characterization (malignant/indeterminate/benign), and diagnosis were given.

Lesion tracking

After the completion of the PET/CT combined assessment, the largest lesions (up to 10) were tracked across all imaging modalities by comparing all maps/images that were obtained together with assessment results recorded in the CRF. Based on the PET/CT lesion numbers, which served as references, the numbers of the respective lesions detected with arterial phase corrected PET, portal-venous phase corrected PET, late phase corrected PET, precontrast corrected PET, and CT (all phases combined) were identified. The occurrence of additional (false positive) or not detected lesions in any of the assessments was documented.

Safety

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

Statistical Methods:

Demographics and Baseline Characteristics:

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

Efficacy:

In general, frequency distribution tables (N, %) were produced for categorical data and summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data.

Exploratory statistical testing were performed on the $p = 0.05$ level.

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Statistical Methods (continued):
Efficacy (continued):

PET: Standard Uptake Values (SUV)
SUV values as obtained by the 4 different types of attenuation-corrected PET maps were presented for lesions, for surrounding tissue, and for lesion-to-background ratios (= lesion SUV / surrounding-tissue SUV) by summary statistics. Differences between the attenuation corrections were analyzed by a repeated measures ANOVA. Separate analyses were performed for maximum and for mean SUV values obtained.

The absolute differences between precontrast CT corrected and the 3 different types of postcontrast CT corrected SUV values of lesions and of lesion-to-background ratios (= postcontrast value minus precontrast value) were calculated and presented by summary statistics. Two-sided 95% confidence intervals were computed for the mean of the differences.

The percent changes between precontrast CT corrected and the 3 different types of postcontrast CT corrected SUV values of lesions and of lesion-to-background ratios (= (postcontrast value minus precontrast value) x 100/precontrast value) were calculated and presented by summary statistics. Two-sided 95% confidence intervals were computed for the mean of the percent changes.

PET: Qualitative Assessments
Results of the assessments of the quality of contrast and delineation based on the separate assessments of PET maps were presented separately for the 4 different types of attenuation-corrected PET maps. Differences between the attenuation corrections were analyzed by a Friedman Chi-Square test.

Results of the paired assessments of PET maps were presented separately for the 3 pairs that were evaluated. A Wilcoxon signed rank test was used to analyze the results for each pair. The number and percentage of patients for whom additional information would lead to a change in diagnosis were presented.

Results of the assessments of artifacts obtained during paired assessments of PET maps were presented separately for the 3 pairs that were evaluated. Differences between the attenuation corrections were analyzed by a Friedman Chi-Square test.

CT: Contrast Density Measurements
The contrast densities (HU) measured were presented by the 4 different CT modalities for lesions, for surrounding tissues and for the lesion-to-background ratios (lesion value / surrounding-tissue value) by summary statistics.

The absolute differences in contrast densities between precontrast phase and the 3 different postcontrast phases of lesions and of lesion-to-background ratios (postcontrast value minus precontrast value) were calculated and presented by summary statistics. Two-sided 95% confidence intervals were computed for the mean of the differences.

The percent changes in contrast densities between precontrast phase and the 3 different postcontrast phases of lesions and of lesion-to-background ratios ((postcontrast value minus precontrast value) x 100/precontrast value) were calculated and presented by summary statistics. Two-sided 95% confidence intervals were computed for the mean of the percent changes.

Lesion Detection
Based on the combined PET/CT assessment, the number of true positive, false positive and false negative lesions was presented for all PET and CT modalities.
True positive (TP) lesion: lesion that was detected in the combined PET/CT assessment as well as in the single modality.
False positive (FP) lesion: lesion that was not detected in the combined PET/CT assessment but was described as a lesion in the single modality.
False negative (FN) lesion: lesion that was detected in the combined PET/CT assessment but not in the single modality.
True negative (TN) lesion: lesion that was neither detected in the combined PET/CT assessment nor in the single modality.

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Statistical Methods (continued):
Efficacy (continued):

Lesion Characterization
Based on the joined PET/CT assessment, the number of true positive, false positive, and false negative characterization findings were presented for all PET and CT modalities. A malignancy was considered a positive finding. Worst cases were assumed for malignant lesions according to combined PET/CT that were not detected or which were found to be indeterminate by a single modality. Benign lesions not detected were rated as "true negative" as it is accepted that PET does not identify benign lesions and since benign lesions are not in the focus of this study.

Safety:
Safety data were summarized for all subjects dosed with the study agent (SAF population). Safety analysis was based on the analysis of adverse events. Adverse events were summarized by the Medical Dictionary for Regulatory Activities (MedDRA) primary System Organ Class (SOC), MedDRA preferred term, intensity, and causal relationship to the investigational product.

Summary and Conclusions:

Demographics:
The study population comprised approximately twice as many male patients (N = 19) than female patients (N = 9). The mean age of the study population (N = 28) was 58.0 ± 11.7 years (range: 35.0 to 77.0 years), the mean weight was 81.7 ± 15.4 kg, and the mean height was 174.8 ± 7.7 cm. All study patients were white.

Exposure to Investigational Product and/or Comparator Product:
All 28 patients received the planned total volume of 100 mL Iomeprol 400 according to protocol.

Efficacy:

Technical Adequacy of PET maps and CT images
The arterial-phase CT corrections of PET maps of 1 patient were technically inadequate due to misalignment caused by inspiration instead of expiration during arterial-phase CT. The data from this set was not included in the efficacy analyses. The Investigator considered all other PET maps and all pre-and postcontrast CT images adequate for diagnostic evaluation.

PET: Quantitative Assessments
Maximum and mean SUVs were higher in the liver lesions than in the normal liver parenchyma. The mean values of the mean SUV in lesions and surrounding tissue were lowest in precontrast CT corrected PET maps and highest in portal-venous phase CT corrected PET maps. Prior to administration Iomeprol 400, the mean values of the mean SUV were 2.70 ± 0.5 for surrounding tissue and 5.50 ± 2.5 for the average over up to 3 largest lesions of a patient. In portal-venous phase CT corrected PET maps the mean SUV values were 2.93 ± 0.4 for surrounding tissue and 5.81 ± 2.6 for the average over up to 3 largest lesions of a patient. The mean lesion-to background ratios (LBRs) for the average over up to 3 largest lesions of a patient were highest in precontrast CT corrected PET Maps (2.11 ± 1.1) and lowest in portal-venous phase CT corrected PET maps (2.04 ± 1.1). The differences in mean SUVs and LBRs between the 4 different types of attenuation corrections were statistically significant ($p<0.05$, repeated measures ANOVA) for surrounding tissue, the largest lesion of a patient, and the average over up to 3 largest lesions of a patient. The highest mean increase in mean SUV was only 5.56% and was obtained for portal-venous phase corrections of the average over up to 3 largest lesions when compared to precontrast CT corrections. The corresponding LBR decreased by a mean of 3.37%.

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Summary and Conclusions (continued):
Efficacy (continued):

PET: Qualitative Assessments
The quality of contrast and delineation on PET maps was assessed as insufficient in 4 out of 21 PET positive patients for all types of CT corrections. For the remaining 17 PET positive patients, quality of contrast and delineation was assessed as excellent (N = 10) or good (N = 7). There were no differences between the precontrast CT corrected and the 3 types of postcontrast CT corrected PET maps.
Artifacts related to CT correction were mainly seen in arterial-phase CT corrected PET maps (when compared to precontrast CT corrected PET maps; 55.0% of PET positive patients had arterial-phase CT corrected PET maps with minor artifacts. However, all artefacts were seen in the veins of upper thorax at the side of contrast injection; none of these artifacts were located in the anatomical area of interest and, thus, the artifacts had no impact on liver diagnosis. No artifacts were seen in the portal-venous phase CT corrected PET maps of any patient and only 1 out of 21 (4.8%) late-phase CT corrected PET maps showed minor artifacts.
Image quality of PET maps was found to be equal between the precontrast CT correction and all 3 types of postcontrast CT corrections.

CT: Quantitative Assessments
Contrast density measurements (HU) in liver lesions (individual average over up to 3 largest lesions of a patient) and corresponding surrounding liver parenchyma showed that mean contrast densities were higher in the surrounding tissue than in the lesions on all CT scans. The mean contrast density of precontrast images was 53.4 HU in surrounding tissue and 38.6 HU in lesions. After administration of Iomeprol 400, the mean contrast density in normal tissue and in lesions was highest in the portal-venous phase (104.7 HU in tissue and 76.5 HU in lesions). The mean percent increase in contrast density between precontrast and portal-venous phase images was 90.6% for liver lesions. The contrast between lesion and surrounding tissue was highest in the precontrast images (mean LBR: 0.7 ± 0.2) and in the portal-venous phase images (mean LBR: 0.7 ± 0.3), and the contrast was lowest in arterial phase images (mean LBR: 0.9 ± 0.3).

CT: Qualitative Assessments
The Investigator rated the image quality of the CT images excellent for 10 patients (35.7% of 28 patients), good for 16 patients (57.1%), and fair for 2 patients (7.1%). None of the images was of poor or insufficient quality.

Lesion Detection
Eighty-nine lesions were identified with the combined PET/CT. Two of the 89 lesions were not detected by the single CT modality and were considered false negative. There were no differences in lesion detection between the pre- and postcontrast corrected PET maps: 45 lesions were not found in any PET modality (PET negative lesions), 44 lesions were detected in precontrast CT, portal-venous phase CT, and late-phase CT corrections. Due to the technical inadequacy of the arterial phase CT corrected PET map of 1 patient, only 43 lesions were detected with this type of PET modality.

Lesion Characterization
Up to 5 lesions were characterized per patient. By using combined PET/CT, 25 lesions were characterized as benign and 50 as malignant. With regard to detection of malignancy, the number of false negative lesions was higher with PET alone than with CT alone (i.e. 13 vs. 4), whereas the number of false positive lesions was higher with CT alone than with PET alone (i.e. 15 vs. 1). There were no differences in the characterizations and assessments of malignancy between the pre-and postcontrast CT corrections (apart from the arterial phase CT corrections, where 2 lesions could not be described due to technical inadequacy of 1 PET map).

Safety:
One patient (3.6%) experienced a total of 2 adverse events which were of moderate intensity and were assessed by the Investigator as possibly related to the administration of the investigational product. The symptoms (nausea and dizziness) were pharmaceutically treated and the patient recovered within a short period of time.

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Conclusions:

The following conclusions can be drawn from this phase IV, open-label, exploratory study on the use of Iomeprol 400 in PET/CT in patients with suspected liver malignancies:

- The administration of Iomeprol 400 led to an increase in contrast density in liver lesions and surrounding tissue. The highest mean contrast densities were obtained in the portal-venous phase, i.e. 104.7 HU in surrounding tissue and 76.5 HU in lesions.
- The mean values of mean and maximum SUVs of liver lesions and surrounding tissue were usually higher on postcontrast than on precontrast CT corrected PET maps and the differences between the attenuation corrected PET maps were statistically significant in repeated measures ANOVA (exception: mean values of the maximum SUV of the largest lesion of a patient).
- Despite the statistically significant differences in SUVs between the 4 types of CT corrections, the largest mean increase in mean SUV was only 5.56% when comparing portal-venous phase to precontrast CT corrected PET maps with regard to the individual average of SUV over up to 3 largest lesion of a patient.
- The observed increase in SUVs on postcontrast CT corrected PET maps had no influence on the clinical interpretation. The assessments of quality and contrast of delineation, image quality, lesion detection, and lesion characterization led to the same results for pre- and postcontrast CT corrected PET maps.
- No previously unknown risks of Iomeprol 400 were detected.

Overall, the results of this study showed that Iomeprol 400 can be used to enhance contrast on CT images in combined PET/CT without compromising the clinical interpretation of the PET maps. Although SUVs were increased in postcontrast CT corrected PET maps, these increases were not clinically relevant. In addition, radiation exposure of the patient may be reduced because the performance of a precontrast CT scan may not be necessary in contrast enhanced PET/CT.

Date of Report: August 28, 2009