

11.6 Study P829-23

Phase 2, P829-23 (Volumes 1.35-1.37)

Study Period: September 25, 1995 to November 28, 1996

Formulation: Market Formulation

Population: Patients with somatostatin receptor bearing tumors

Phase II Clinical Trials Evaluating the Safety and Efficacy of Technetium Tc 99m P829 in the Detection and Localization of Somatostatin Receptor-Expressing Tumors: Dose-Ranging.

Objectives:

- 1) To evaluate the safety and tolerance of a single intravenous administration of Technetium Tc 99m P829 in patients with somatostatin receptor-expressing tumors;
- 2) To evaluate Technetium Tc 99m P829 for its ability to detect and localize somatostatin receptor-expressing tumors by gamma scintigraphy in patients with tumors also evaluated by indium In¹¹¹ pentetreotide;
- 3) To assess safety and target/background uptake ratio as a function of different doses of P829 peptide and technetium 99m; and
- 4.) To establish the optimal dose or dose range for P829 peptide and technetium 99m for Phase 3 trials by blinded image evaluation and region-of-interest analysis to determine quantitative tumor target/background uptake ratios.

Design: This is a prospective, multicenter, randomized single dose administration, within patient controlled clinical trial to evaluate multiple peptide and radioactive dose levels. A total of 36 patients with either clinically documented or suspected somatostatin receptor-expressing tumors will be enrolled. Each patient will randomly receive one of nine possible combinations of Technetium 99m activity and P829 peptide doses. Focal planar images of the primary and secondary tumor (as determined from the pentetreotide scan) sites will be performed at 15 minutes, 75 minutes, and 18-24 hours post-injection. SPECT images will be performed immediately following the second set of focal planar images. Additional images may be taken at any time within the first 6 hours post-dosing. A blinded read of the images will be carried out with regions of interest identified for target to background calculations. Comparison of the three activity levels and peptide levels will be performed. Dose response relationship will be evaluated using appropriate statistical tests. Comparisons between target to background ratios for P829 images and In-111 pentetreotide images will be performed. Safety will be assessed by monitoring vital signs, hematology and serum chemistries and adverse event reporting.

Patient Population: A total of 36 patients who present with a somatostatin receptor-expressing tumor or metastasis as demonstrated by a recent (**within 4-10 days**) positive Indium In-111 pentetreotide study, will be enrolled (**changed to: within a reasonable time frame**). All patients will be 18 years or older and will provide written informed consent. Reasons for exclusion from the study are listed below.

Exclusion Criteria:

- Patient is pregnant or breast feeding;
- Patient is unable to remain quietly supine or has any medical condition that prohibits gamma scintigraphy;
- Patient has received another investigational agent within 30 days prior to study enrollment;
- Patient is currently receiving somatostatin (or somatostatin analog) therapy;
- Patient, if enrolled, would become the fifth patient at this center with a given tumor type;
- Patient has an anticipated life expectancy at the time of enrollment of less than 60 days; or
- Patient has received indium In¹¹¹ pentetreotide within the **previous 4 days**.
(**Changed to: 48 hours prior to the intended administration of technetium Tc 99m P829.**)

Dose: Three different peptide and mCi doses will be prepared. Each patient will receive a single dose of one of the following randomly assigned doses:

- 5mCi at 10, 20, 50µg peptide level
- 10mCi at 10, 20 and 50µg peptide level
- 20mCi at 10, 20, and 50µg peptide level

Imaging Procedure: Focal planar images of the primary and secondary tumor sites will be performed at 15 minutes, 75 minutes and 18-24 hours post-injection. For suspected chest, abdominal or pelvic tumors, SPECT images following the completion of the second set of planar images will be performed. Additional whole body, planar and/or SPECT images may be performed at any time during the first 6 hours post-injection. Imaging data will be collected in the digital format, as well as on film. Patients will be requested to void between imaging sessions and the bladder will be shielded during imaging.

Image Read: The images will be evaluated by a blinded reader who will be blinded to the patient's clinical history. Regions of interest will be defined on the Tc99m P829 images, based on lesions identified by the In-111 pentetreotide study. Target to background ratios will be calculated for the regions drawn.

Comment: *No further description of the blinded read was found in the text portion of the original protocol, however, the information that follows was taken from the sample case report forms submitted. It is not stated whether the blinded readers were blinded to the dose.*

It appears from the case report forms that uptake will be graded for all images (focal planar and SPECT) for 6 body regions as follows: head/neck, chest, abdomen, pelvis, upper extremities and lower extremities. The grading scale is defined as:

- 1- Negative: no area of abnormality in this region
- 2- Indeterminate: abnormal area of uptake cannot be determined
- 3- Positive: abnormal isotope localization suggesting tumor/metastasis
- N/A- not applicable: images not obtained in this region

Safety: Safety assessments include the following:

- Vital signs recorded at baseline 10, 30 and 90 minutes post-injection.
- Hematology and clinical chemistry parameters will be measured at baseline and at 18-24 hrs post-injection.
- Adverse events will be monitored for at 10, 30 and 90 minutes and 18-24 hr post-injection.

Vital Sign Parameters: Systolic and diastolic blood pressure, heart rate, respiratory rate, and oral temperature.

Hematology Parameters:

Hematocrit, Hemoglobin, Platelet Count, Complete Blood Count, Differential White Blood Cell Count.

Blood Chemistry Parameters:

Albumin, globulin, calcium, chloride, phosphorus, potassium, sodium, carbon dioxide, glucose, blood urea nitrogen (BUN), uric acid, creatinine, total and direct bilirubin, creatinine phosphokinase, lactic dehydrogenase (LDH), alkaline phosphatase, serum glutamic-oxaloacetic transaminase

Statistical

Efficacy: Comparison among the three peptide levels will be made by combining data obtained from all three activity levels and comparisons among the three activity levels will be made by combining the data obtained from all three peptide levels. Using appropriate statistical tests, it will be determined if there is any dose-response relationship between the target/non-target ratio and the peptide dose or the activity dose.

Target/background ratios for Tc99m P829 also will be compared with target/background ratios for In-111 pentetreotide. If Tc99m P829 identifies any lesions not previously suspected by the In-111 pentetreotide, then the results of correlative testing will be described and assessed in relationship to peptide and activity levels, anatomic location and tumor type.

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Results:

Protocol Deviations: The inclusion criteria were changed, however, the investigator at site 3 followed the original inclusion criteria which required that patients have the In-111 pentetreotide study performed within 4 days of the Tc-99m P829 scan. Due to this, one patient at site 3 did not meet this criterion but the Sponsor approved enrollment.

Disposition: Forty-six patients were enrolled at six study sites. All patients but one completed the study. The patient, who did not complete the study, completed the P829 imaging portion but refused the In-111 pentetreotide study. Therefore, 46 patients were evaluated for safety and 45 patients were evaluated for efficacy. The largest percent of patients (36.9%) had carcinoid tumor. Four patients (8.7%) had small cell lung cancer.

Extent of Exposure: The P829 kit was reconstituted with 1mL of sodium pertechnetate and was not heated. For those patients who received the 5 mCi dose, the range of activity injected was 4.09 to 5.90 mCi. For the 10 mCi and 20 mCi doses, the ranges of activity injected were 6.84-11.0 and 16.3-21.7 mCi respectively. All doses administered had greater than 85% radiochemical purity. The Lot # for the to-be-marketed formulation used for this study were 9509M01A, 9509M01B, 9509B01B and 9509B01D. The distribution of patients receiving each dose level can be found below in the Table 1.

Table 1: Dosage Distribution: Number of Patients at Each Dose Activity and Peptide Level

		Activity (technetium 99m)		
		5 mCi	10 mCi	20 mCi
Number of patients at each activity level	n	15	15	16
Patients at 10 µg/dose peptide	n (%)	5 (33%)	5 (33%)	5 (31%)
Patients at 20 µg/dose peptide	n (%)	5 (33%)	5 (33%)	5 (31%)
Patients at 50 µg/dose peptide	n (%)	5 (33%)	5 (33%)	6 (38%)

Data source: Abstracted cross tabulation of activity by peptide level from Appendix 16.2.11
 Note: Percentages are based on total number of patients.

Data Source: Sponsor's Text Table 10-B, Vol. 1.38, pg. 065.

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Demographics: No major differences were seen in patient demographics. A summary of demographic descriptive statistics can be found in Tables 2 and 3.

Table 2: Demographics

Patients	Statistic	All Patients	Activity Level			Peptide Level		
			5mCi	10mCi	20mCi	10µg	20µg	50µg
	n	46	15	15	16	15	15	16
Age (yrs)	mean	55.3	56.8	52.9	56.2	57.1	55.6	53.3
	median	56.5	57.0	51.0	56.5	62.0	51.0	55.5
	Std. Err.	2.14	3.53	2.74	4.63	3.91	4.23	3.17
	Min	26	29	32	26	26	31	29
	Max	81	75	69	81	75	81	70
Gender								
	n (%)	21 (46%)	8 (53%)	6(40%)	7 (44%)	4 (27%)	8(53%)	9(56%)
	n (%)	25 (54%)	7 (47%)	9(60%)	9 (56%)	11(73%)	7(47%)	7(44%)
Race								
Caucasian	n	34	12	12	10	11	11	12
Black	n	5	1	2	2	1	2	2
Hispanic	n	2	0	1	1	1	0	1
Nat. Amer.	n	0	0	0	0	0	0	0
Asian	n	2	0	0	2	1	0	1
Other	n	3	2	0	1	1	2	0

Data Source: Sponsor Table 2.0, 2.1, 2.2

Table 3: Demographics Con't.

Parameter	Statistic	Male	Female
Weight	n	21	23
	Mean	80.4	70.7
	Median	79.0	67.0
	Std. Err.	3.5	3.4
	Min.	37.7	50.9
	Max.	116.0	113.6
Height	n	21	23
	Mean	175.9	161.9
	Median	177.8	162.6
	Std. Err.	1.5	1.5
	Min.	154.3	152.4
	Max.	182.9	177.8

Data Source: Sponsor Table 2.3

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Efficacy:

Comment: A comprehensive statistical plan was not provided in the original protocol and was not amended to the IND. In the study report protocol, a post-hoc statistical plan was added. This post hoc analysis may or may not be valid. The following gives a brief description of what was done.

Technetium Tc 99m P829 images were to be assessed relative to the indium In¹¹¹ pentetreotide images for the same region. Efficacy analyses included the following:

- Correlation scoring by region between Technetium Tc 99m P829 images and indium In¹¹¹ pentetreotide images;
- Per-patient agreement between Technetium Tc 99m P829 images and indium In¹¹¹ pentetreotide images; and
- Percent agreement on positive regions, as assessed by Technetium Tc 99m P829 images and indium In¹¹¹ pentetreotide images.

Imaging results were evaluated by investigator assessment and by blinded reader assessment. A majority blinded reader score was used to evaluate imaging assessment results for the purpose of the study report.

Blinded Image interpretation by body region

Three blinded readers reviewed the focal planar and SPECT images for focal uptake per body region. Regions assessed include left and right sides of the following regions: head/neck, chest, abdomen, pelvis, upper extremities, lower extremities. The Sponsor presented the agreement between the Tc99m P829 and In-111 pentetreotide based on a majority read for the blinded readers. See Table 4 below. The table also provides investigator read interpretations. The Sponsor's conclusion from this table is that the highest agreement rate was seen in the chest and pelvis and the lowest agreement rate was seen in the abdomen.

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Table 4: Agreement between Technetium Tc 99m P829 and Indium In¹¹¹ Pentetreotide by region Investigator and Blinded Read* Interpretations

Interpretation	Head and Neck		Chest		Abdomen		Pelvis	
	Investigator	Blinded Readers	Investigator	Blinded Readers	Investigator	Blinded Readers	Investigator	Blinded Readers
Focal Planar Images Source Tables 5.0, 6.0.4 Patients Assessed Agreement between Technetium Tc 99m P829 and indium In ¹¹¹ pentetreotide	N (%)	22 91%	26 88%	39 86%	29 83%	40 69%	28 95%	40 89%
SPECT Images Source Tables 5.1, 6.1.4 Patients Assessed Agreement between Technetium Tc 99m P829 and indium In ¹¹¹ pentetreotide	N (%)	12 75%	17 74%	13 77%	36 68%	30 55%	27 94%	22 80%
Whole Body Images Source Table 5.2 Patients Assessed Agreement between Technetium Tc 99m P829 and indium In ¹¹¹ pentetreotide	N (%)	32 91%	33 83%	0	0	33 62%	33 93%	0

*Majority Blinded Read Scores were based on three blinded nuclear medicine practitioners' scores for each region.

Source: Sponsor Text Table 11-B

Comment: The Sponsor's comparison of Tc99m P829 to In 111 pentetreotide does not provide enough information to draw any conclusions regarding the usefulness of this drug in detecting somatostatin receptor bearing tumors. The results in all regions except for the right abdomen reported more than half the patients as having a negative P829 test which was in agreement with a negative pentetreotide test. There is no truth by which to judge the validity of the negatives as being true negatives versus false negatives. In review of the data, the agreement rates listed in the Sponsor's table appear valid based solely on their reproducibility from the referenced tables. When looking at the individual blinded reads, the number of patients with a positive P829 in agreement with a positive pentetreotide was very low and very variable from one blinded reader to the next. Of those that disagreed, for the majority blinded read, most cases were reported as P829 negative and pentetreotide positive. Without a standard by which to confirm the presence or absence of disease, this comparison is clinically meaningless.

Image Interpretation by Activity Level:

Both the investigator read and blinded majority read did not show any one dose being superior. All correlation scores for the blinded read were equivalent at the three dose levels.

Image Interpretation by Peptide Level:

Sponsor's results: Based on the majority blinded read tables, the Sponsor concluded, that for the focal planar images, there was more agreement between the blinded reader's scores for Tc 99m P829 images and the In 111 pentetreotide images at the higher peptide levels.

Per-Patient Rates of Agreement:

The three activity levels tested and three peptide levels tested produced similar per-patient agreement between the Technetium Tc 99m P829 and indium In¹¹¹ pentetreotide images as evaluated both by the investigators and by the blinded readers. Per-patient agreement on a positive diagnostic rating revealed that none of the 3 dose levels were clinically superior to the others.

Region-of-Interest:

Target to background ratios were obtained for 15 of the 46 patients studied. None of the three technetium 99m activity levels, or the three P829 peptide levels tested were clinically superior to the other doses tested. Target to background ratios for Octreoscan were collected but not analyzed.

Sponsor's Efficacy Conclusions:

There was no one combination of the nine of the possible combinations of the three activity levels (5, 10, and 20 mCi) and the three peptide levels (10, 20, and 50 µg), that was clinically superior to the other combinations tested.

Comment:

The Sponsor looked at correlation scoring between Tc 99m P829 and In 111 pentetreotide images to assess for dose response for different activity and peptide levels for the majority blinded read per body region. The design of the study did not allow for the ability to distinguish subtle changes due to the small sample sizes used for the individual doses. The information obtained did not provide adequate analysis to determine any dose response relationship. The tables provided by the sponsor failed to show the individual blinded reader's scores, therefore, the ability to compare the variability between the readers is lost. The tables which appear to focus only on the majority blinded read give no basis for comparison to a standard of truth. Lack of truth (disease present or absent) upon which to make a definitive comparison leads to a weak foundation upon which to base a Phase 3 trial. The mere fact that P829 image read matched or disagreed with In-111 pentetreotide does not provide any clinically meaningful information on which to base a Phase 3 trial. Given that the pivotal trials for this NDA do not mimic what took place in this study, the information gained from this study does not support the pivotal trials in terms of dose selection or efficacy hypotheses generation. Due to the marked variability in the correlation scoring between doses (both radioactivity and peptide doses) no clear advantage could be distinguished for any one particular dose. The data does not provided a dose response relationship for either radioactivity or peptide level.

The Sponsor's conclusion for peptide dosing cannot be substantiated for two reasons: 1.) The Sponsor did not provide the individual blinded reader data for review, but rather, only provided the majority blinded read data and 2.) In most cases less than half the patients had SPECT images assessed, therefore, the sample size is too small to reliably show any dose response when compared with the focal planar image reads.

If intent was to identify somatostatin receptor expressing tumors, patients with confirmed presence of tumor should have been enrolled to test this hypothesis. Patients were enrolled solely based on suspicion of tumor, thus resulting in a large proportion of the patient population testing negative. A confirmed patient population is needed in order to generate hypotheses.

Safety:**Deaths: 0****Withdrawals due to an Adverse Event: 0****Serious Adverse Events: 0****Severe Adverse Events: 0**

Adverse Events: Three adverse events were reported in one patient. These adverse events included diarrhea, vomiting and nosebleed. The adverse events were reported as having an onset of 30 hours post Tc99m P829 dosing and were not considered to be drug related by the Sponsor. The diarrhea and vomiting resolved within 24 hours of onset and the nosebleed resolved within 4 days of onset. No events were considered serious or required treatment.

Hematology:

These data show a statistically significant mean decrease in WBC count at 18-24 hours; this decrease was not clinically significant. The mean and median values were well within the normal limits at both time points, and the minimum and maximum values were similar. There were no clinically or statistically significant mean changes in any of the other hematology parameters.

There were only two patients with treatment-emergent clinically significant hematology parameters.

Patient 829-23-3-05, an 80-year-old female (20 mCi technetium 99m, 20 µg P829 peptide injection) had a low pre-injection hemoglobin (10.2 g/dL) and hematocrit (30.2%), and had an 8% decrease in hemoglobin and hematocrit post-injection. Her 18-24 hour post-injection hemoglobin (9.4 g/dL) and hematocrit (27.3%) were clinically significant as defined in the protocol. This patient remained clinically stable and completed the indium In¹¹¹ pentetreotide images without event.

Patient 829-23-6-05, a 29-year-old male (5 mCi technetium 99m, 50 µg P829 peptide injection) had a thymus tumor mass removed on the day of his pre-injection laboratory assessments; his hematocrit (43.4%), hemoglobin (15.7 g/dL), RBC count (4.8 M/uL), and lymphocytes (29.8%) were normal pre-injection. The post-injection laboratory assessments were obtained after his surgical procedure. The change in these laboratory assessments were clinically significant, as defined in the protocol; hematocrit (29.2%), hemoglobin (10.2 g/dL), RBC count (3.2 M/uL), and lymphocytes (9.2%). Blood loss during surgery and subsequent compensatory fluid shifts were surmised, by the Sponsor, to have contributed to these changes.

Clinical Chemistry Parameters:

There was a statistically significant mean increase in uric acid at 18-24 hours; this increase was not clinically significant because both the pre and post-injection values were well within the normal range. The pre and post-injection minimum and maximum uric acid values were similar, as well. There was a statistically significant mean decrease in LDH at 18-24 hours; however, decreases in this parameter are not normally considered clinically relevant. Additionally, both the pre and post-injection mean LDH values were elevated. Since elevations in LDH are seen in a variety of conditions including malignancy, pulmonary disease, and liver disease, it is not unexpected to find an elevation in mean LDH values in a population with clinically documented tumors and/or metastasis. It is worth noting that the median pre and post-injection LDH values (which are less affected by a single extreme value) were within normal limits.

There were five patients with treatment-emergent clinically significant clinical chemistry parameters. The Sponsor's synopsis for each case can be found below.

Patient 829-23-2-03, a 70-year-old male (5 mCi technetium 99m, 50 µg P829 peptide injection) had a normal pre-injection BUN (22 mg/dL) which increased to 30 mg/dL, the clinically significant cutpoint, at 18-24 hours post-injection. This patient's creatinine level was normal (1.1 mg/dL) pre-injection and remained normal (1.1 mg/dL) post-injection.

Patient 829-23-2-09, a 64-year-old diabetic female on glyburide (10 mCi technetium 99m, 50 µg P829 peptide injection) had a high pre-injection glucose (164 mg/dL). Her glucose increased and the change was considered clinically significant (252 mg/dL) at 18 - 24 hours post-injection. The elevated glucose level was consistent with her preexisting diabetes

Patient 829-23-3-04, a 75-year-old diabetic female on diabinese (10 mCi technetium 99m, 50 µg P829 peptide injection) had a high pre-injection glucose (175 mg/dL). Her glucose increased and was clinically significant at 18-24 hours post-injection (294 mg/dL). Her elevated glucose level was consistent with her preexisting diabetes.

Patient 829-23-3-02, a 58-year-old male (10 mCi technetium 99m, 10 µg P829 peptide injection) had clinically significant post-injection evaluations of alkaline phosphatase, LDH and total bilirubin, with no pre-injection values available. The patient had metastatic liver disease, which may have caused these laboratory abnormalities.

Patient 829-23-6-02, a 73-year-old male (5 mCi technetium 99m, 20 µg P829 peptide injection) had a high pre-injection non-fasting glucose (178 mg/dL). This patient's non-fasting serum glucose remained elevated (203 mg/dL) at his post-injection assessment, however both glucose values are medically similar, reflective of this patient's non-fasting state.

Laboratory values were evaluated based on the amount of peptide administered and no clinically significant effects were seen for all three peptide levels tested.

Comment: In review of the mean change from baseline data for each clinical chemistry parameter, only two parameters had statistically significant changes from baseline values: uric acid and LDH. The change from baseline for uric acid was a mean increase of 0.21mg/dl. No conclusions can be drawn from this due to the fact that individual patient uric acid data were not provided by the Sponsor. The change from baseline for LDH was a mean decrease of 25 U/L. The mere fact that this change was a decrease in LDH, does not have any clinical meaning. However, it appears that a significant number of patients had elevated liver function tests at the time of enrollment. Of the 46 patients enrolled, 28 had at least one liver function test elevated at baseline. Of those 28, 13 had multiple liver function tests abnormally high at the time of enrollment. Post-injection liver function test results for these patients did not show any particular trends that would be considered clinically significant.

All other laboratory parameters did not show any trends that would lead to any special follow-up in future studies.

Urinalysis: There were no notable increases in the incidence of patients with post-injection urinalysis abnormalities for any of the parameters measured.

Vital Signs: There were no clinically meaningful or statistically significant mean changes in any of the vital sign parameters at any post-injection timepoint. Two patients were noted to have a change in pulse by 20 bpm. One patient (23-5-08) had a drop from 90 bpm to 70 bpm at the 30 minute assessment period. The patient's pulse rose to 80 bpm for the subsequent assessment times. The second patient (23-5-04) had an increase in pulse from 60 bpm to 80 bpm at all post-injection timepoints. The Sponsor did not view either of these changes as clinically significant.

Comment: Patient 23-5-04 also had a drop in systolic and diastolic pressure which accompanied the rise in pulse. The patient's systolic pressure dropped from 136 mmHg to 126 mmHg and the diastolic dropped from 80mmHg to 68 mmHg. The Sponsor did not report any adverse events for this patient. Patient 23-5-08 had a gradual decrease in systolic blood pressure which accompanied the drop in pulse. The patient's systolic pressure at baseline was 130 mmHg and at subsequent assessment timepoints was 120, 116 and 124 mmHg. The patient's baseline pulse was 90bpm with subsequent values as follows: 80, 70, and 80 bpm. No symptoms or adverse events were reported. Diastolic blood pressure and respiration rate remained relatively constant.

No clinically significant trends in the vital sign data were seen.

Sponsor's Conclusions:

A single injection of technetium Tc 99m P829 was well tolerated by all patients in this study. All nine possible combinations of the three technetium 99m activity levels and the three levels of P829 peptide were equally well tolerated.

The sponsor chose 50 µg as the optimal P829 peptide dose and 20 mCi as the optimal technetium 99m dose to use in Phase 3 trials. Dose selection was based on the safety results from this study and the clinical requirements for an effective imaging agent. The 50 µg peptide dose was chosen because this study did not reveal any safety advantages of the lower doses, 50 µg provides a larger capacity to carry the radiolabel as it decays than lower peptide doses, and 50 µg is the minimal dose that can be used to make a "rugged kit" practical for clinical use with the current manufacturing procedures. The 20 mCi dose of technetium 99m was chosen for the following reasons:

- A 20 mCi dose falls within the lower end of standard technetium 99m dose range which is 15-30 mCi
- The radiation dosimetry of P829 is non-limiting at 20 mCi, making this a safe dose in terms of radiation exposure.
- The 20 mCi dose promotes larger photon flux than lower doses. Maximum photon flux is necessary for SPECT imaging which is required in the evaluation of lung nodules.

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In conclusion, a single IV injection of technetium Tc 99m P829 (5, 10, and 20 mCi technetium 99m; 10, 20, and 50 µg P829 peptide) was safe and well tolerated at all of the nine possible combinations of P829 peptide dose and technetium 99m activity level. The three doses of P829 peptide (10, 20, and 50 µg) and technetium 99m (5, 10, and 20 mCi) assessed in this study all produced similar results for the target-to-background uptake ratio, blind image evaluation, and region-of-interest analysis. Overall, none of the three technetium 99m activity levels or the three P829 levels tested was clinically superior to the other doses tested in this study, however pharmacological advantages favored selection of 50 µg peptide and 20 mCi as the optimal dose of this product.

Reviewer's Conclusions:

Design/Efficacy: The purpose of this study was to determine the dose that provided the best safety and efficacy profile. The Sponsor's dose response measurement was the rate of agreement between Tc99m P829 imaging and In 111 pentetreotide imaging. Given that this study was looking at somatostatin receptor-expressing tumors, it seems plausible for the Sponsor to have selected In 111 pentetreotide as the standard against which to measure their product. However, the clinical relevance of agreement between Tc99m P829 and In 111 pentetreotide is questioned given In 111 pentetreotide's sensitivity of 85% and specificity of 68%. Regardless of their clinical meaning, rates of agreement between the two tests could function as an acceptable design for this dose ranging Phase 2 study. Given this design, however, the Sponsor tested nine different dose combinations randomly within a patient population rather than testing different doses within the same patients. This practice coupled with the small patient population failed to provide any dose response trends between the doses utilized. If the Sponsor would have given a group of patients multiple different doses separated by adequate washout periods, then the rate of agreement could have been assessed more vigorously, possibly leading to trends in the data to support a safe and efficacious dose for the Phase 3 trials. From this trial there is no supportive data for the peptide dose selected for the Phase 3 trials.

The Sponsor's rationale for choosing the largest Tc99m dose is sound and makes sense that greater radioactivity will provide better count statistics for better images, however, the lack of dose response in the target to background ratios does not support the need for the largest millicurie dose.

The rationale for the selection for the 50 µg peptide dose is suspect. The patient population (16 patients) to receive this dose level is not large enough to prove its safety for use in a large trial.

The addition of a post-hoc statistical analysis is troublesome, however, its potential impact on the study results is reduced due to the fact that this dose ranging study did not provide useful information regarding proper selection of dose.

Safety: As stated above, three adverse events were reported to occur in a single patient. These events occurring 30 hours post drug administration makes them less likely to be drug related. All events were self-limiting and did not require treatment.

All vital sign assessments and clinical laboratory data in this small population did not show any significant trends to suggest the need for increased vigilance in safety screening.

Formulation: The formulation studied was the unheated dose preparation of the market formulation. The equivalence (efficacy and safety) between the heated and unheated dose preparations has not been adequately addressed by the Sponsor, therefore, this study does not provide applicable supportive data.

Reviewer's Conclusions: The rationale for the radioactivity dose selection is sound. The rationale for the peptide dose selection is not understood. No apparent safety trends were identified. The impact of the use of the unheated dose preparation on efficacy and safety results is not known.

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Phase 3
Study P829-30A

11.7 Study P829-30A

Phase 3 P829-30A : Volumes 1.39-1.49, Additional Information submitted after filing with letter dates 7/9/98 and 7/28/98.

Study Date: February 29, 1996 to July 8, 1997

Formulation: _____ **Market Formulation**

Population: Patients with Neuroendocrine Tumors

Title: A Multicenter, Within-Patient, Phase 3 Trial To Evaluate The Safety And Efficacy Of Technetium Tc 99m P829 For Detection And Localization Of Somatostatin Receptor-Expressing Neuroendocrine Tumors.

Objectives:

1. Evaluate the safety and tolerance of a single intravenous administration of Technetium Tc 99m P829 in patients presenting with evidence of neuroendocrine tumor; and
2. Evaluate the efficacy of Technetium Tc 99m P829 for detection and localization of somatostatin-receptor expressing tumors by gamma scintigraphy, using the final institutional clinical diagnosis as the standard for comparison.

Design: This is a multi-center, single dose, within-patient comparative, open-label study enrolling approximately 120 patients with a documented clinical history of Neuroendocrine tumor thought to express somatostatin receptors. Each patient was to have undergone an Indium In-111 Pentetreotide study not less than 7 days and not more than 60 days prior to study participation or to be scheduled to undergo an In-111 Pentetreotide study within 36 hours to 14 days following Technetium Tc99m P829 study. Each patients will receive approximately 20mCi of Tc99m P829 (50µg of peptide). Focal planar imaging will begin approximately 1 hour post-administration and be repeated at 3-6 hours post-administration. SPECT imaging will be performed following the 3-6 hour focal planar images. Whenever possible, a tissue sample from surgical treatment of biopsy procedure will be obtained. Each tissue sample obtained will have in vitro somatostatin receptor binding assays performed. Both In-111 Pentetreotide images and Tc-99m P829 images will be read by three blinded Nuclear Medicine physicians. Images sets (Pentetreotide and P829) will be randomized and independently read by readers blinded to patient identity or history. Image sets will be evaluated for the presence or absence of uptake in each of the following areas according to hemisphere (right and left) for a total of 12 anatomic regions: head/neck, chest, abdomen, pelvis, upper extremities and lower extremities. The degree of abnormality will be scored as either negative (no abnormal localization suggesting tumor) or positive (abnormal localization suggesting tumor). The final institutional diagnosis will be recorded on the case report form specifying the presence or absence of tumor or metastasis in the 12 anatomic regions.

The diagnostic modality used to obtain the final diagnosis will be recorded. The primary indicator of efficacy will be the patient-based rate of agreement with the final institutional diagnosis.

Agreement between the institutional diagnosis and Tc99m P829 or In-111 Pentetreotide will occur if there is presence of tumor in at least one of the 12 body regions considered or if there is absence of disease for all 12 regions of the body. Secondary indicators of efficacy include region-based rates of agreement with the final diagnosis and patients and region-based sensitivity and specificity calculations for both Tc99m P829 and In-111 Pentetreotide. Safety will be assessed by vital sign, laboratory parameters and adverse event monitoring. Please see Table 1 for the timing of procedures.

Table 1. Time Table of Events

	Pre-Dose	+5 min.	+30 min.	+1 hour	+3-6 hrs.	+18-24 hrs.	+24 hrs.
Vitals	√	√	√	√	√		√
Labs	√				√		√
Adverse Events				√			√
In-111 Imaging						√	
Tc-99m P829 Imaging				√	√		

Dose: An intravenous injection of the heated market formulation of Tc99m P829 will be administered. Patients will receive a single administration of 20mCi of Tc99m P829 (50µg of P829 peptide). Approximately 6 mCi of Indium In-111 Pentetreotide (10 µg of peptide) will be intravenously administered.

Results:

Protocol Deviations:

- Patients 1-2 and 1-7 had changes in their Octreotide therapy regimen that did not conform to inclusion/exclusion criteria.
- Patients 5-5, 5-7, 5-8, 10-5 and 10-9 did not have an indium In-111 Pentetreotide study performed at the specified time intervals prior to and following Tc99m P829 imaging.
- Patient 2-4 had been previously entered in the study
- As per the Sponsor, there were 12 patients which had In-111 Pentetreotide imaging at times other than specified by the protocol. These patients were identified as deviating from the protocol, however were included in the efficacy analysis.

Disposition:

A total of 117 patients were enrolled at 9 United States sites and at 4 European sites (sites 8, 10, 11 and 14). The disposition by study site can be found in Table 2. Sites 9 and 15 did not enroll any patients. All but two patients (2-4 and 11-2) were considered evaluable for purposes of the efficacy analysis. These two patients did not have an In-111 pentetreotide scan, therefore, were excluded.

Table 2. Disposition by Study Site

Study Site	Number of Patients Enrolled
1	19
2	5
3	9
4	23
5	10
6	4
7	14
8	1
10	12
11	10
12	4
13	4
14	2
TOTAL	117

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Data Source: Sponsor Text Table III, Vol.50.

Demographics: Summary statistics for age weight, height, gender and race are provided for all patients and for the evaluable patient population in tables 3-4. Mean age of the efficacy evaluable population was 55.7 years with a range of 22.8 to 81.9 years. Approximately 52% of the evaluable population were female and 48% were male. The majority (90%) of the population was Caucasian. Since there was only a difference of 2 patients between the intent-to-treat (ITT) population and efficacy evaluable population, demographic information for the efficacy evaluable population was representative of that for the ITT population.

TABLE 3. SUMMARY STATISTICS FOR AGE, WEIGHT AND HEIGHT.						
		N	MIN.	MAX.	MEAN	STD. DEV.
Age (yr)	All Patients	117	22.8	81.9	55.7	13.6
	Evaluable Patients	115	22.8	81.9	55.9	13.6
Height (cm)	All Patients	117	132.1	193.0	169.3	10.8
	Evaluable Patients	115	132.1	193.0	169.2	10.8
Weight (kg)	All Patients	117	40.9	128.6	73.8	17.2
	Evaluable Patients	115	40.9	128.6	73.8	17.2

Data Source: Sponsor Text Table VIII., Vol. 139, pg. 058.

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TABLE 4. DISTRIBUTION OF GENDER AND RACE.

		All Patients		Evaluable Patients	
		N	%	N	%
GENDER	Female	62	53.0	60	52.2
	Male	55	47.0	55	47.8
	TOTAL	117		115	
RACE	Black	7	6.0	7	6.1
	White	106	90.6	104	90.4
	Other	4	3.4	4	3.5
	TOTAL	117		115	

Data Source: Sponsor Text Table IX., Vol. 139, pg. 059.

Carcinoid tumor was the most common tumor type evaluated in this study. A total of 5 patients (4%) had lung tumor. The remainder of the breakdown of tumor type studied can be found in table 5.

TABLE 5. PATIENT DISTRIBUTION OF PRESENTING TUMOR TYPES.

TYPE	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
Carcinoid	49	41.9	48	41.7
Endocrine Pancreatic	6	5.1	6	5.2
Gastrinoma	6	5.1	6	5.2
Medullary Thyroid Carcinoma	5	4.3	5	4.3
Growth-Hormone Producing Pituitary	3	2.6	2	1.7
Islet Cell	3	2.6	3	2.6
Neuroendocrine	3	2.6	3	2.6
Paraganglioma	3	2.6	3	2.6
Small Cell Lung Cancer	3	2.6	3	2.6
Large Cell Lung Cancer	2	1.7	2	1.7
Pheochromocytoma	2	1.7	2	1.7
Vipoma	2	1.7	2	1.7
Other	3	2.6	3	2.6
ANY TYPE ¹	87	74.4	85	73.9

¹ Numbers represent patients confirmed with these tumors. Percentages are relative to all patients (117) or to total evaluable patients (115).

Data Source: Sponsor Text Table X., Vol. 139, pg. 060.

Tumor type breakdown for those patients presenting with lung tumor can be found in table 6.

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Table 6. Tumor Type Localized in the Lungs

TUMOR TYPE	N
Carcinoid	6
Large Cell	2
Small Cell	3
Ectopic ACTH Secreting Tumor	1

Data Source: Table 3, Vol. 1.44, Appendix 16.2, pg. 015.

A table showing the location of tumor presentation can be found below in table 7. The majority of lesions presented in either the liver or gastrointestinal tract. Ten percent of the efficacy evaluable population had tumors presenting in the lungs (n=12).

TABLE 7. PATIENT DISTRIBUTION OF PRESENTING TUMOR LOCATIONS.				
LOCATION	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
Liver	23	19.7	23	20.0
Gastrointestinal	22	18.8	22	19.1
Lung	12	10.3	12	10.4
Pancreas	10	8.5	10	8.7
Thyroid	3	2.6	3	2.6
Adrenal	3	2.6	3	2.6
Pituitary	3	2.6	2	1.7
CNS	1	0.9	1	0.9
Mediastinum	1	0.9	1	0.9
Unknown ¹	1	0.9	1	0.9
Other ²	10	8.5	9	7.8

¹ Unknown represents tumors that were confirmed by methods that did not include location, e.g. clinical chemistry.

² Other includes tumors whose locations were indicated on the CRF but were not one of the categories listed in the above table.

Data Source: Sponsor Text Table XI., Vol. 1.39, pg. 061.

The modality used to diagnose patients at the time of enrollment can be found in table 8. Computed tomography was the most common modality used (71%) followed by In-111 pentetretotide. Biopsy was performed in 42% of the efficacy evaluable population. Of the 12 patients presenting with tumor in the lung, diagnostic modalities used to confirm disease include CT (10 patients), X-ray (6 patients), In-111 pentetretotide (5 patients), biopsy (5 patients), MRI (2 patients), surgery (6 patients), hormone levels (2 patients) and clinical chemistry levels (1 patient).

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TABLE 8. PATIENT DISTRIBUTION OF MODALITIES EMPLOYED IN INITIAL DIAGNOSIS OF PRESENTING TUMORS ON A BY-PATIENT BASIS.				
MODALITY	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
CT	84	71.8	82	71.3
In 111 Pentetreotide	67	57.3	66	57.4
Biopsy	49	41.9	49	42.6
Surgery	49	41.9	48	41.7
Hormone Levels	42	35.9	41	35.7
Ultrasound	27	23.1	26	22.6
MRI	27	23.1	27	23.5
X-ray	22	18.8	21	18.3
Clinical Chemistry	19	16.2	18	15.7
PET	1	0.9	1	0.9
Other	30	25.6	30	26.1

Data Source: Text Table XII, Vol. 1.39, pg. 061.

A listing of the number of patients receiving somatostatin analog therapy during this study can be found in table 9. None of the 12 patients presenting with tumor in the lung were on somatostatin analog therapy.

TABLE 9. DISTRIBUTION OF SANDOSTATIN® OR OTHER SOMATOSTATIN ANALOG USAGE.				
MEDICATION	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
Sandostatin® (octreotide)	18	15.4	16	13.9
Lanreotide	2	1.7	2	1.7
NONE	97	82.9	97	84.3
TOTAL	117		115	

Data Source: Sponsor Text Table XIII., Vol. 1.39, pg. 063.

The last treatment received by each patient presenting with lung tumor and the timing of that treatment can be found in table 10.

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Table 10. Type and Timing of Treatment Received Prior to Enrollment

PATIENT	PREVIOUS TREATMENT	TIME SINCE TREATMENT
1-11	Surgery	< 1 month
1-14	Surgery	> 5 years
1-15	Surgery	1-3 months
1-18	None	
2-1	Surgery	1-3 months
3-6	Radiation Chemotherapy	3-6 months 1-3 months
4-1	Surgery	1-3 months
4-12	Surgery Radiation Chemotherapy	1-5 years 1-5 years 1-5 years
4-22	Surgery Radiation	6 months- 1 year 3-6 months
12-2	Chemotherapy	6 months - 1 year
12-3	Chemotherapy	< 1 month
13-2	Surgery	1-5 years

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Drugs for the treatment of peptic ulcers, taken by 24 evaluable patients (21%), and agents acting on the renin-angiotensin system, taken by 13 evaluable patients (11%), were the most commonly used classes of concomitant medications, followed by beta-blocking agents, thyroid preparations and antidepressants, which were each taken prior to the Technetium Tc 99m P829 study by approximately 10% of evaluable patients. Seventy-eight evaluable patients (67.8%) had taken at least one medication within 24 hours of the study. The most common concomitant medication classes taken by patients in the lung tumor group were diuretics and decongestants (2 patients each).

MEDICATION	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
Treatment of Peptic Ulcers	24	20.5	24	20.9
Thyroid Preparations	11	9.4	11	9.6
Beta-Blocking Agents	13	11.1	12	10.4
Agents Acting on Renin-Angiotensin System	13	11.1	13	11.3
Opioids	10	8.5	10	8.7
Antidepressants	11	9.4	11	9.6
Low-Ceiling Diuretics, Thiazides	10	8.5	10	8.7
Other	70	59.8	69	60.0
Any Medication (one or more medications)	79	67.5	78	67.8
TOTAL	117		115	

Data Source: Sponsor Text Table XV., Vol. 139, pg. 064.

The indium In 111 pentetreotide study was to have been performed at least 7 days prior but not more than 60 days prior to the Technetium Tc 99m P829 study or, alternatively, the indium In 111 pentetreotide study could have been performed between 36 hours and 14 days following the Technetium Tc 99m P829 study. A listing of the dates of injections of Technetium Tc 99m P829 and indium In 111 pentetreotide is provided in Table 12.

TIMING OF INDIUM In 111 PENTETREOTIDE	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
> 60 d. prior	4	3.4	4	3.5
60 d. to 7 d. prior	47	40.2	47	40.9
6 d. prior to < 1 d. post	6	5.1	6	5.2
1 d. post to 14 d. post	56	47.9	56	48.7
> 14 d. post	2	1.7	2	1.7
No study performed	2	1.7	0	0
TOTAL	117		115	

Data Source: Sponsor Text Table XVII., Vol. 1.39, pg. 066.

Efficacy Results: Image results (negative, positive for tumor or NA-images not acquired) were reported for six anatomical regions per body side. All blinded reads were compared to the final institutional clinical diagnosis, which was considered definitive. Blinded read results per region for Tc99m P829 and In-111 pentetreotide when compared to the institutional diagnosis were categorized as follows (table 13):

	PATIENT	READER NUMBER(S)
Indium In 111 pentetreotide images considered to be of nondiagnostic quality.	7-3	2
	12-1	2
Technetium Tc 99m P829 images considered to be of nondiagnostic quality.	6-1	2

Data Sponsor: Sponsor Text Table VI., Vol. 1.39, page 057.

Patient-based rate of agreement, sensitivity and specificity for the blinded read compared to the final institutional diagnosis was considered the primary efficacy analysis. Region-based rates of agreement were also performed. When In-111 pentetreotide results were incomplete, best case was assumed and when Tc99m P829 results were incomplete, worst cases was assumed with regard to the institutional diagnosis.

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Comment: Patient rates of agreement are not the best means to assess the efficacy of this drug. Region-based rates of agreement will give better one-to-one site agreement, therefore, patient based rates of agreement were not reviewed. Sensitivity and specificity calculations are the endpoints recommended for this efficacy analysis. These calculations were performed for the patient-based analysis but not for the region-based analysis. Therefore, the efficacy analysis performed by the Sponsor by region will be briefly reported but it is recommended that sensitivity and specificity calculations be performed.

The diagnostic results across all sites for the twelve anatomic regions for the institutional diagnosis can be found in table . Of the evaluable patients, the majority presented with abdominal tumors. Distribution of tumor type observed in the final institutional diagnosis can be found in tables 14-15. The most common tumor found in 46 patients was carcinoid tumor.

TABLE 14. DISTRIBUTION OF FINAL INSTITUTIONAL CLINICAL DIAGNOSIS FOR PRESENCE OF TUMOR FOR EVALUABLE PATIENTS.

REGION	SIDE	DIAGNOSIS			TOTAL PTS WITH DX
		NO TUMOR NUMBER (%)	TUMOR NUMBER (%)	NOT DONE	
Head/Neck	L	99 (90.8)	10 (9.2)	6	109
	R	102 (93.6)	7 (6.4)	6	109
Chest	L	95 (84.1)	18 (15.9)	2	113
	R	92 (81.4)	21 (18.6)	2	113
Abdomen	L	68 (59.1)	47 (40.9)	0	115
	R	47 (40.9)	68 (59.1)	0	115
Pelvis	L	105 (93.8)	7 (6.3)	3	112
	R	104 (92.9)	8 (7.1)	3	112
Upper Extremity	L	74 (97.4)	2 (2.6)	39	76
	R	73 (96.1)	3 (3.9)	39	76
Lower Extremity	L	64 (98.5)	1 (1.5)	50	65
	R	64 (98.5)	1 (1.5)	50	65
All Patients		23 (20.0)	92 (80.0)	0	115

Data Sponsor: Sponsor Text Table XIX, Vol. 1.39, page 068.

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TABLE 15. PATIENT DISTRIBUTION OF TUMOR TYPES ACCORDING TO FINAL INSTITUTIONAL CLINICAL DIAGNOSIS FOR EVALUABLE PATIENTS.

TUMOR TYPE	N	%
Carcinoid	46	40.0
Endocrine Pancreatic	5	4.3
Gastrinoma	11	9.6
Medullary Thyroid Carcinoma	4	3.5
Adrenal	3	2.6
Growth-Hormone Producing Pituitary	2	1.7
Islet Cell	3	2.6
Neuroendocrine	2	1.7
Paraganglioma	4	3.5
Large Cell Lung Cancer	2	1.7
Pheochromocytoma	3	2.6
Vipoma	2	1.7
Insulinoma	1	0.9
Parathyroid	1	0.9
ANY TYPE	86	74.8

Data Sponsor: Sponsor Text Table XX., Vol. 1.39, page 069.

Indium In 111 pentetreotide was used in determining the final institutional clinical diagnosis for 106 of 115 evaluable patients (92.2%). Seventy-seven patients (67.0%) had a CT scan. Biopsy and surgery were both used for approximately 10% of evaluable patients.

Patient-based Analysis: The patient-based rates of agreement and sensitivity calculations per blinded reader reveal that In-111 pentetreotide consistently outperformed (statistical significance seen) Tc99m P829. For specificity calculations, no statistical difference was seen between the two modalities when compared to the final institutional diagnosis. (See Volume 1.39, page 71-74 for actual results)

Agreement rate per Region: Both modalities, Tc99m P829 and In-111 pentetreotide were comparable for the following regions: head/neck, pelvis and extremities. A statistical difference between the modalities was seen in the chest and abdominal region with In-111 pentetreotide showing greater agreement with the final institutional diagnosis. The percent agreement per blinded reader were summarized as a range in the table 16. Please note the variability in the size of the sampled population per region. Few positive results were seen in the extremity regions therefore the agreement rates were almost exclusively a function of the true negatives. A kappa statistic to assess the interreader variability for the region-based analysis was not performed.

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Table 16. Agreement Rates for Tc99m P829 and In 111 Pentetreotide

Anatomic Region	N	Agreement Range (%)	Statistical Significance*
Head/Neck			
Tc99m P829	76-105	91-92	No
In-111 pentetreotide	89-106	86-90	
Chest			
Tc99m P829	110-113	81-82	Yes
In-111 pentetreotide	109-113	89-93	
Abdomen			
Tc99m P829	112-115	47-63	Yes
In-111 pentetreotide	112-115	71-82	
Pelvis			
Tc99m P829	109-112	85-93	No
In-111 pentetreotide	106-111	87-90	
Upper Extremities			
Tc99m P829	28-64	93-97	No
In-111 pentetreotide	38-74	97-99	
Lower Extremities			
Tc99m P829	19-54	89-96	No
In-111 pentetreotide	19-59	90-98	

Data Source: Text Tables XXV, XXVI, XXVII-XXX, Vol. 1.39. *McNemar's χ^2 statistic

Subgroup Analysis: This analysis used the patient-based aggregate reader agreement rates.

Patients presenting with primary lung cancer: Fourteen patients presented with suspicion of tumor of the lung. Of the 14, 10 were found to have a positive final institutional clinical diagnosis versus 4 who were found not to have lung cancer by final institutional clinical diagnosis (Table 17). No significant difference in agreement rates between the blinded readers and the final institutional diagnosis was seen between the two modalities.

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Final Diagnosis	N	Reader	Agreement @ (N / %)		
			P829	Octreo	p-value
POS	10	1	7 (70)	8 (80)	1.000
		2	7 (70)	5 (50)	0.683
		3	7 (70)	7 (70)	0.617
		AGG.	9 (90)	9 (90)	0.479
		INV.	7 (70)	7 (70)	0.683
NEG	4	1	4 (100)	4 (100)	--
		2	3 (75)	4 (100)	1.000
		3	4 (100)	4 (100)	--
		AGG.	4 (100)	4 (100)	--
		INV.	4 (100)	4 (100)	--

@ Agreement for patients for whom final diagnosis = POS corresponds to sensitivity; agreement for patients for whom final diagnosis = NEG corresponds to specificity. POS = positive for tumor, NEG = negative for tumor. AGG = Aggregate blind read and INV = Investigator's reading.

Data Source: Sponsor Test Table XXVIA, Vol. 1.39, page 080.

Age: The agreement rate for In-111 pentetretotide was statically significantly better than that for Tc99m P829 when compared to the final institutional diagnosis for patients under the age of 65 years. No difference was seen above the age of 65 years.

Gender: The agreement rate for In-111 pentetretotide was statically significantly better than that for Tc99m P829 when compared to the final institutional diagnosis for both male and female patients.

Race: The agreement rate for In-111 pentetretotide was statically significantly better than that for Tc99m P829 when compared to the final institutional diagnosis for Caucasian patients. No difference was seen in all other races grouped together.

Patients with Abnormal Renal and Liver Function: Seven evaluable patients (6%) had abnormal renal function and 38 evaluable patients (35%) had abnormal liver function. The agreement rate of Technetium Tc 99m P829 results with final institutional clinical diagnosis was at least 25% lower than the corresponding agreement rate of indium In 111 pentetretotide results for both subgroups (normal and abnormal) defined by renal function and for both subgroups (normal and abnormal) defined by liver function.

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