

Phase 2
Study P829-00

11.3 Study P829-00

Phase 2, 829-00 (Volume 1.74)

Date of Study: November 24, 1994 to March 11, 1996

Formulation: [redacted] Investigational Formulation

Population: Patients with Neuroendocrine tumors or Lymphomas

Title: Open-Label Study Assessing the Imaging Efficiency of Diatech Technetium Tc 99m P829, a Technetium Labeled Somatostatin Receptor Binding Peptide, in Patients Diagnosed with Neuroendocrine Tumors or Lymphoma.

Objectives:

- 1) To evaluate the feasibility of imaging somatostatin-bearing tumors with technetium Tc 99m P829.
- 2) To determine the general biodistribution and tumor kinetics of technetium Tc 99m P829.
- 3) To evaluate the safety of a single administration of technetium Tc 99m P829.
- 4) To compare the efficacy of imaging tumors bearing somatostatin receptors employing technetium Tc 99m P829 with that of Indium In 111 Pentetreotide.

Design: This is an open label, unblinded, single center Phase 2 study to assess the safety, general biodistribution and the ability of Tc99m P829 to localize in neuroendocrine tumors and lymphomas expressing somatostatin receptors. Patients 18 years or older with neuroendocrine tumors or lymphomas will be enrolled. Any female patients who are lactating or pregnant will be excluded. Patients on somatostatin analog therapy will be enrolled but not to exceed 50% of the total population. Patients will receive an intravenous injection of 8-15mCi of Tc99m P829 followed by focal planar imaging performed at 15-30, 60-90 minutes and 2.5-3 hours post injection. To help enhance detectability of small lesions, SPECT imaging will be performed of the chest and abdomen at 1.5-2.5 hours post injection. Efficacy will be evaluated by comparison of P829 image results to all other clinically relevant diagnostic and follow-up procedures including MRI, CT, Indium In-111 Pentetreotide, clinical signs and symptoms, relevant blood and urine chemistries and surgical/biopsy analyses. Safety and tolerance of the agent will be assessed by active observation for any change in the patient's condition during the course of the study. No statistical analysis plan was provided.

Results:

Protocol Deviations:

- 1.) No more than three patients of a specific tumor type were to be studied however, 21 of the 23 patients enrolled had melanoma.
- 2.) SPECT images were to be acquired on all patients, however, only 2 patients had SPECT images performed.

Disposition/Demographics: Twenty-three patients were enrolled in the study. Of the 23, 21 patients had melanoma and 2 patients had pituitary tumors. All patients completed the study and were included in the safety analysis. Patient 17 did not have clinical truth established, therefore, was excluded in the patient-based agreement analysis. Patient demographic characteristics can be found in Sponsor's Tables 1 and 2 below.

TABLE 1. SUMMARY STATISTICS FOR AGE, WEIGHT AND HEIGHT.					
	N	MIN.	MAX.	MEAN	STD. DEV.
AGE (yr)	23	27.0	78.0	53.1	15.0
WEIGHT (kg)	23	48.0	104.0	71.1	14.1
HEIGHT (cm)	23	151.0	182.0	165.3	8.4

Data Source: Sponsor's Text Table II, Vol. 1.74, page 022.

TABLE 2. DISTRIBUTION OF GENDER.			
		N	%
GENDER	Female	14	60.9
	Male	9	39.1
	TOTAL	23	

Data Source: Sponsor's Text Table III, Vol. 1.74, page 022

The most common abnormalities occurring on physical exam were abnormal lymph nodes in six patients (26.1%) and head/neck abnormalities in three patients (13.0%). Only one patient had a history of a chronic inflammatory process at the time of the study.

Efficacy Results: Specific uptake of Tc99m P829 as compared with background activity in the region of the documented tumor was considered as a positive result. The primary indicator of efficacy was the patient-based rate of agreement between Tc99m P829 results and the patient's true disease state (clinical truth) as listed in Table 3.

TABLE 3. PATIENT-BASED AGREEMENT BETWEEN TECHNETIUM Tc 99m P829 RESULTS AND CLINICAL TRUTH.			
Clinical Truth	technetium Tc 99m P829 Results		Total
	Negative	Positive	
Negative	5	1	6
Positive	2	14	16
Total	7	15	22*

*This includes patient 17 even though Clinical truth not defined, Data Source: Sponsor's Text Table VIII, Vol. 1.74, page 027, Table 18, Vol. 1.74, page 0126.

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The patient-based rate of agreement between Tc99m P829 and clinical truth was 86.4%. The sensitivity of Tc99m P829 in detecting neuroendocrine tumors (majority of the tumors were melanoma) was 87.5% and specificity was 83%. Patient 4 and 5 had a nonfunctioning pituitary adenoma and parathyroid adenoma, respectively, which were reported as negative on Tc99m P829 images. Patient 5 also had a pituitary tumor, a gastrinoma and a pheochromocytoma for which both clinical truth and Tc99m P829 results were positive. For those 21 patients with melanoma, the patient-based rate of agreement between Tc99m P829 and clinical truth was 95%. The sensitivity of Tc99m P829 in detecting melanoma was 100% and specificity was 83%.

No patients had an indium In 111 pentetreotide study, therefore, there is no comparison made between Tc99m P829 and In 111 pentetreotide.

Sponsor's Efficacy Conclusions: Technetium Tc 99m P829 appeared to have potential for gamma scintigraphic imaging of neuroendocrine tumors. The patient-based agreement rate between technetium Tc 99m P829 results and clinical truth was 86.4% (95% CI = 64.0 - 94.1%). Considering the subset of 20 melanoma patients for whom clinical truth was known, the patient-based agreement rate between technetium Tc 99m P829 results and clinical truth was 95% (95% CI = 73.1 - 95.5%).

Safety Results:

Deaths: 0

Withdrawals due to an Adverse Event: 0

Serious Adverse Events: 0

Severe Adverse Events: 0

Extent of Exposure: A summary of the mCi and peptide exposures seen in this study are provided in Table 4 below. The injected radioactive dose administered ranged from 9.5 to 20.0mCi of Tc99m. The range of P829 peptide administered was 40 to 87 µg. Lot used was 94183-13/28.

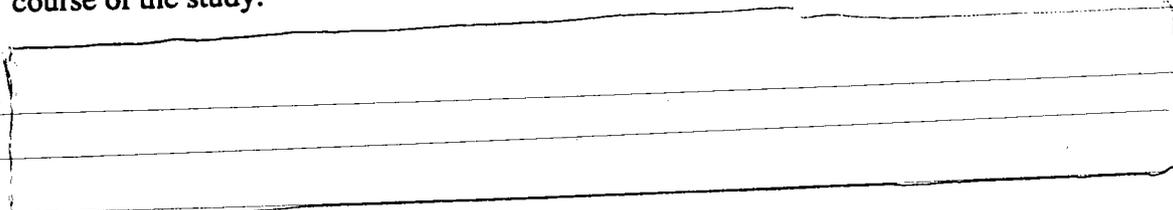
TABLE 4. SUMMARY STATISTICS FOR TECHNETIUM Tc 99m P829 DOSING.					
	N	MIN.	MAX.	MEAN	STD. DEV.
RADIOLABELING EFFICIENCY	23	91.0	98.9	93.1	2.1
VOLUME INJECTED (mL)	23	0.1	0.4	0.2	0.1
INJECTED RADIOACTIVITY (mCi)	23	9.5	20.0	14.9	3.0
PEPTIDE INJECTED (µg)	21*	40.0	87.0	60.1	14.5

* Not recorded for 2 patients, Data Source: Sponsor's Text Table VII, Vol. 1.74, pg.025.

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No systemic or local response was seen after administration of Tc99m P829.
No blood work or vital sign monitoring was planned in this study.

Sponsor's Safety Conclusions: Technetium Tc 99m P829 appeared safe in patients diagnosed with neuroendocrine tumors. No adverse events were reported during the course of the study.



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Phase 2
Study P829-20

11.4 Study P829-20

Phase 2, P829-20 (Volume 1.75)

Study Period: February 5, 1995 to September 30, 1995

Formulation: _____ Investigational Formulation

Population: Patients with Neuroendocrine tumors and Lymphomas

Title: Phase 2 Clinical Trial Evaluating the Safety and Efficacy of Technetium Tc99m P829 in the detection and Localization of Neuroendocrine Tumors and Lymphomas.

Objectives:

- 1) To evaluate technetium Tc 99m P829 for its ability to detect and localize Neuroendocrine tumors and Lymphomas.
- 2) To evaluate the dose response profile of technetium Tc 99m P829 over the following dose ranges:
 - 8 mCi, with at least three patients at each peptide level (5, 20, and 50 μ g)
 - 12 mCi, with at least three patients at each peptide level (5, 20, and 50 μ g)
 - 15 mCi, with at least three patients at each peptide level (5, 20, and 50 μ g)
- 3) To compare the efficacy of imaging neuroendocrine tumors or lymphomas using technetium Tc 99m P829 with correlating clinical diagnostic information (CT scan, MRI, surgery, biopsy, pathology reports, chemistry reports, etc.).
- 4) To evaluate technetium Tc 99m P829 for its general safety and tolerance in human patients.

Design: This is a multicenter (5 sites), non-randomized, unblinded Phase 2 clinical trial designed to evaluate the ability of Tc99m P829 to detect and localize neuroendocrine tumors and lymphomas as well as to evaluate the dose response profile when three different activity and peptide levels are administered. At least 36 patients 18 years or older with a clinical indication of neuroendocrine or lymphoma will be enrolled. Female patients who are pregnant or lactating will be excluded. Patients on somatostatin therapy may be enrolled up to half the total population. Three dose levels (8, 12 and 15mCi) and varying peptide levels (5, 20 and 50 μ g) will be studied. Each investigator will do at least one subject at each dose and peptide level for a total of at least nine patients. After dose administration, focal planar, SPECT and whole body imaging will be performed over 3 hours post-administration. Images will be evaluated for clinical significance, optimal radioactive dose and peptide level and for any unique or unexpected findings. Image results will be assessed for their correlation with known initial diagnostic procedures and any follow-up procedures which may include In-111 pentetreotide, surgery/biopsy and subsequent pathology. Safety assessments include adverse event reporting, vital signs assessments and local and systemic response monitoring. No statistical analysis plan was identified.

Table 1. Time Table of Events

PARAMETER	PRE-STUDY	POST- STUDY					
		15 mins.	45 mins.	60 mins.	1-1.5 hrs.	1.5-2.5 hrs.	3+ hrs.
Abbreviated history and Physical Exam	√						
Adverse Events		√	√	√	√*	√	√
Vital Signs		√		√	√*		
Imaging Focal Planar Whole Body SPECT			√		√	√	√

*assessments to be performed at 1.5 hrs.

Results:**Protocol Violations/Deviations: As per Sponsor**

A change in the formulation of the P829 kit (addition of EDTA to P829 vial) was submitted to FDA on July 20, 1995. Dose levels did not allow for statistical assessment of differences between the administered doses of technetium Tc 99m. Therefore, efficacy data were not analyzed. Sites 1, 3, 5, and 6 enrolled fewer than nine patients each and therefore did not complete the dose ranging as indicated in the protocol.

Sites 2 and 4 enrolled more than nine patients each, but did not provide at least one patient at each dose and peptide level.

Site 2 did not record oral temperature for any patients at any time point post-injection. The exclusion criteria specified that a patient should not be the third patient with a tumor type already studied at each institution. Approval for enrollment of three patients at site 2 who did not meet this criteria (patient 829-20-2-11 with a diagnosis of small cell lung cancer, and patients 829-20-2-13 and 829-20-2-14 with a diagnosis of non-Hodgkin's lymphoma) was granted by Diatide, Inc.

Disposition: A total of 42 patients were enrolled at 6 clinical sites. All patients received a single administration except one patient which had two injections (patient 5-01/5-04). All patients successfully completed the study.

Demographics:

The demographics for the 42 patients enrolled can be found in Tables 2-4.

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Table 2. Demographics

PARAMETER	
N	42
Age	
Mean	52.5
Range	19-87
Gender	
Male	23 (55%)
Female	19 (45%)
Race	
Caucasian	29 (24%)
Black	3 (7%)
Oriental	10 (24%)

Data Source: Appendix 16.2.1, Vol. 1.75, Pg. 0207

Table 3. Demographics

PARAMETER	MALE	FEMALE
Height (cm)		
Mean	177	162
Range	156-191	145-175
Weight (kg)		
Mean	82	67
Range	48-119	43-113

Data Source: Appendix 16.2.1, Vol. 1.75, Pg. 0207

APPEARS THIS WAY
ON ORIGINAL**Table 4. Tumor Type**

TUMOR TYPE	n
Carcinoid	11
Lymphoma	
Non-Hodgkin's	5
Hodgkin's	4
Small Cell Lung Cancer	6
Melanoma	2
Pheochromocytoma	4
Pancreatic	
Insulinoma	1
Gastrinoma	4
Non-functioning	1
Paragnaglioma	1
Pituitary Tumor	1
Medullary Thyroid Cancer	1
Parathyroid Adenoma	2
TOTAL	43

Data Source: Appendix 16.2.2, Vol. 1.75, pg. 0212.

Efficacy: No efficacy evaluation was performed. Investigator's comments were provided in data listing format but not summary format, which would allow for review.

Safety:

Extent of Exposure: The total dose injected ranged from 7.24 to 19.4 mCi of Tc99m P829. Total injected dose ranges for each planned mCi dose were 7.24 to 8.4 mCi for the 8mCi dose, 9.4 to 13.5 mCi for the 12 mCi dose and 12.4 to 19.4 for the 15 mCi dose. The number of patients that received a particular dose can be found in Table 5.

Table 5. Dosage Distribution: Number of Patients at Each Dose Activity and Peptide Level

		Activity (technetium 99m)		
		8 mCi	12 mCi	15 mCi
Number of Patients	n	9	16	17
Patients at 5 µg/Dose Peptide	n (%)	7 (17%)	9 (21%)	4 (10%)
Patients at 20 µg/Dose Peptide	n (%)	1 (2%)	4 (10%)	8 (19%)
Patients at 50 µg/Dose Peptide	n (%)	1 (2%)	3 (7%)	5 (12%)

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

Data Source: Sponsor Text Table 12A, Vol. 1.75, pg. 035.

Deaths: 0

Withdrawals due to an Adverse Event: 0

Serious Adverse Events: 0

Severe Adverse Events: 0

Adverse Events: Three patients reported a total of 5 adverse events. Description of the adverse events can be found in Table 6.

Table 6. Adverse Events

Patient Number	Adverse Event	Preferred Term	Onset Post-dose	Duration	Severity	Treatment
1-1	Diarrhea	Diarrhea	10 hrs.	21 hrs.	Mild	None
	Stomach gurgling	Dyspepsia	10 hrs.	21 hrs.	Mild	
	Queasy	Nausea	10hrs.	21 hrs.	Mild	
1-4	Flushing	Vasodilatation	1 min.	1 min.	Mild	None
3-1	Burning during injection	Pain, injection site	Immediate	Unknown	Mild	None

Data Source: Appendix 16.2.15, Vol. 1.75, pg. 0335.

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As per Sponsor patient 1-1 was being treated with Dulcolax and a saturated solution of potassium iodide prior to study, however, the investigator was unable to rule out the study drug as the causative agent. There was no investigator assessment of the relationship to the study drug for the adverse event, flushing. The investigator reported no relationship to study drug for the adverse event, injection site pain.

Vital Signs: Post-injection vital signs included pulse, systolic and diastolic blood pressures, respiration rate, and oral temperature. It should be noted that pre-injection vital signs were not collected in this study. Descriptive statistics at 15 minutes, 60 minutes, and 120 minutes post-injection are summarized in Table 7.

Table 7. Vital Sign Summary Statistics

PARAMETER	POST-INJECTION EVALUATION TIME		
	15 min.	60 min.	120 min.
Pulse (bpm)			
n	41	40	37
Mean	72.2	72.2	73.0
Std. Err.	1.67	1.78	2.09
Range	56-102	52-108	56-122
Systolic Blood Pressure (mmHg)			
n	41	40	37
Mean	128.1	126.4	127.9
Std. Err.	2.77	2.76	3.31
Range	94-160	90-156	90-168
Diastolic Blood Pressure (mmHg)			
n	41	40	37
Mean	78.6	76.8	78.1
Std. Err.	1.73	1.80	1.97
Range	58-105	44-102	45-103
Respiration Rate (Bpm)			
n	41	40	36
Mean	18.5	17.7	18.3
Std. Err.	0.73	0.72	0.80
Range	11-38	11-36	11-38
Temperature (°F)			
n	27	25	23
Mean	98.06	97.79	98.02
Std. Err.	0.129	0.263	0.116
Range	96.8-99.1	92.2-98.8	96.6-98.6

Data Source: Sponsor Table 4.0.

Comment: Since no pre-injection vital sign assessments were made, analysis of the post-injection values offers limited information.

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Sponsor's Conclusions: The safety data suggest that a single injection of technetium Tc 99m P829 at various dose and peptide levels in patients clinically diagnosed with a neuroendocrine tumor or lymphoma was well tolerated by all patients in this study. The incidence of adverse events was limited to five mild events, three of which were felt to be related to concomitant medications. Vital sign measurements recorded over the two hours post-injection showed little mean variation. The safety data, including adverse events and vital sign measurements, suggest that a single injection of technetium Tc 99m P829 was well tolerated by patients at all dose levels.

Reviewer's Discussion:

A change in formulation may to be the reason the Sponsor did not perform an efficacy analysis. No efficacy conclusions can be drawn from this study. A summary of the investigator's findings should have been provided.

Since pre-injection vital sign data was not collected, the effects of the study agent on these parameters could not be adequately assessed. There were limited adverse events reported, all of which may not have been attributed to the study agent.

Reviewer's Conclusions:

No statement regarding the efficacy or safety of Tc99m P829 can be made.

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Phase 2
Study P829-22

11.5 Study P829-22

Phase 2, P829-22 (Volumes 1.76-1.78, Additional information submitted with letter dates 7/9/98, 7/28/98, and 8/26/1998).

Study Period: May 3, 1995 to November 26, 1997

Formulation: [redacted] Investigational & Market Formulation

Population: Patients with somatostatin receptor bearing tumors

Phase 2B Clinical Trial Evaluating The Safety And Efficacy Of Technetium Tc99m P829 In The Detection And Localization Of Somatostatin Receptor Expressing Tumors.

Objectives:

To evaluate Technetium Tc99m P829 for:

- 1.) Its ability to detect and localize tumors known or expected to express somatostatin receptors.
- 2.) To compare the efficacy of imagining of tumor types that may express somatostatin receptors.
- 3.) Safety and tolerance in human subjects.

Design: This is a multicenter, non-randomized, unblinded Phase 2 clinical trial to evaluate the safety and the ability of Tc99m P829 to detect and localize somatostatin expressing tumors. Up to 150 patients that present with a clinical indication of a somatostatin receptor expressing tumors, will be enrolled. Both planar and SPECT imaging will be performed. Investigators will review the images for the presence or absence of Tc 99m P829 uptake in the head/neck, chest, abdomen, upper extremities and lower extremities. Safety will include monitoring of vital signs, blood and urine clinical laboratories and adverse events. The primary efficacy analysis will be the correlation of the investigator's image read results with other confirmatory diagnostic information (including but not limited to: MRI, CT, In-111 Pentetreotide and Clinical information).

Population: Patients 18 years or older with a suspicion of a tumor that may express somatostatin receptors (excluding neuroendocrine tumors and lymphomas) are to be enrolled. All patients must sign an informed consent. Patients will be excluded based on the following criteria:

Exclusion Criteria:

- ◆ Pregnant or lactating females
- ◆ Patients shall not be the seventh patient with a tumor type already studied at each institution without prior approval from Diatide.
- ◆ Patient presents with any condition making the subject unsuited for Technetium Tc99m P829 imaging.

◆ Patient presents with other significant systemic disorders which would significantly increase the possibility of a coincident adverse drug experience or death during or soon after the study period.

Dose: An intravenous dose of approximately 15mCi of Technetium Tc99m P829 (10-50µg) will be administered. Peptide dose levels will be determined by the Principal Investigator. The to-be-marketed formulation will be used in this study. Dose preparation will include a heating step(amended 12/17/96). Dose must exhibit >85% radiochemical purity to be administered.

Imaging: Focal planar images of the chest, abdomen and/or head, as appropriate, should be acquired at 15-60 minutes and 90-180 minutes post-injection. SPECT images of the chest, abdomen and/or head may be acquired in place of the planar images when trying to enhance the detectability of small lesions and metastases. Lesions well localized on planar views will not require SPECT imaging. Additional unscheduled imaging times may be used to obtain whole body planar or SPECT images of other tumors/metastases of the head, chest and/or abdomen.

Image Read: Images will be read by the investigator, who will have full knowledge of the patient's history and diagnostic work-up results. The images will be rated for the presence or absence of Tc99m P829 uptake in each of the following six regions: Head/neck, chest, abdomen, pelvis, upper extremities, and lower extremities. The scale used for scoring the images is the following: 1= negative, 2= indeterminate, 3= positive and N/A= not applicable (images not obtained). Location of uptake in the six regions will be further categorized based on side of the body: A= left, B= right, C= both and D=N/A.

Efficacy Analysis:

Outcome measures will include evaluation of Tc99m P829 images and a comparison of the image results with the results of all other clinically relevant diagnostic and follow-up procedures that contribute to the understanding of the status of the patient's disease. This may include any or all of the following: MRI, CT, Indium In-111 pentetreotide.

Safety Analysis:

Safety and tolerance of the agent will be assessed by evaluation of pre- and post-injection hematology, blood chemistries and urine analysis, vital signs and by observation for adverse events. Vital signs will be assessed at a pre-injection timepoint and at 10, 30 and 90 minutes post-injection. Times for blood collection were not pre-defined.

Amendments: According to the study report there were 7 amendments to this protocol, however, these amendments already appear in the protocol provided as the "original" protocol. It appears that the Sponsor submitted the final amended protocol as the "original" protocol. The changes made were the following:

Two additional sites were added (7/20/95).

Enrollment was increased: from 50 to 150 (12/17/96, 6/11/97).

Safety assessments were added (9/27/95).

Dose range of peptide administered was changed from 5-50 to 10-50 μ g. Patients with any type of somatostatin receptor-expressing tumor, including neuroendocrine tumors and lymphomas were enrolled (12/17/96). Two formulations of the drug kit were used. The quantity of glucoheptonate dihydrate was reduced from 50mg to 5 mg and 100 μ g of EDTA were added. (7/20/95). The addition of a heating step as part of the dose preparation was added (12/17/96). Investigators were added and deleted (8/3/95, 4/26/96, 11/20/97).

Study Results:

Protocol Deviations:

- ◆ Three patients were enrolled prior to confirmation of disease (02-06, 02-39 and 02-68).
- ◆ Study site 2 enrolled patients with neuroendocrine tumors and lymphoma prior to the amendment which allowed their enrollment.
- ◆ Two patients did not have vital sign assessments at the 4 timepoints designated in the protocol (02-02, 02-09)
- ◆ Seven patients had missing pre or post-injection laboratory measurements 02-11, 02-31, 02-38, 02-57, 03-03, 03-04, 03-12).

Disposition: A total of 131 patients were enrolled at 5 clinical sites (4 centers in US, one center in Austria). One patient (04-01) withdrew from the study prior to injection, however, the remaining 130 patients all received at least one Tc99m P829 dose. Nine patients did not complete the study due to lack of collection of safety data. Nine of the 130 patients received multiple doses of Tc 99m P829. A total of 140 doses were administered to 130 patients. The time between doses in these nine patients receiving multiple doses ranged from 2 months to 8 months. The nine patients receiving multiple doses can be found in Table 1. The distribution of patients by study site can be found in Table 2.

Table 1: List of Patients Who Received Multiple Injections of Technetium Tc 99m P829

Initial Patient Assignment	Subsequent Patient Assignment
02-15	02-64
02-23	02-30
02-38	02-78
02-44	02-66
02-47	02-84
02-52	02-87
02-60	02-77, 02-83
02-67	02-80
02-74	02-91

Data Source: Sponsor Text Table 2, Vol. 1.76, pg. 039.

Table 2: Patient Distribution per Site

Clinical Site	Number of Patients
1	5
2	82
3	13
4	31

Data Source: Appendix 16.2.4.1, Vol. 77.

Comment: The text of the study protocol (in the study report) states that 5 study sites were utilized, however, the results section of the study report lists only 4 sites.

Demographics: A summary of the demographic data can be found in Tables 3 & 4.

Table 3: Demographic and Baseline Characteristics (Population: Patients Valid for Safety Analysis)

Variable	All Patients (n = 130)
Age, Mean ± SE (years)	56.4 ± 1.3
Range	(18-86)
Gender, N (%)	
Male	51 (39.2%)
Female	79 (60.8%)
Race, N (%)	
Caucasian	107 (82.3%)
Asian	11 (8.5%)
African American	6 (4.6%)
Hispanic	3 (2.3%)
Other	3 (2.3%)

Source: Section 14.1, Table 14.1.1

Sponsor Text Table 3, Vol. 1.76, pg. 042.

Table 4: Demographics Con't.

Parameter	Statistic	Female	Male
Weight (kg)	n	79	51
	Mean	64.4	76.7
	Range	41-109	41-136
Height (cm)	n	79	51
	Mean	161.6	175
	Range	132-175	160-194

Data Source: Table 14.1.2, Vol. 1.76, pg. 065.

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The most common diagnosis seen was cancer of the breast seen in 33 patients (25%) followed by lung cancer (22%), non-Hodgkin's lymphoma (19%) and Hodgkin's lymphoma (6%). Other diagnoses reported in two or more patients included pancreatic cancer, colon cancer, rectal cancer, adenocarcinoma, thyroid cancer, pheochromocytoma and carcinoid tumor.

Efficacy: The study enrolled patients with a wide variety of tumor types. Given that the indication sought by the Sponsor for the NDA is related to lung cancer, only those patients presenting with lung cancer will be evaluated in this review.

Dose: Two (2-60, 2-67) of the 28 patients with lung cancer received a single dose of Tc99m P829. The Tc99m doses ranged from 6.5 -19.2 mCi. The peptide doses were based on the investigator's discretion and the summary of peptide doses can be found in Table 5. All patients reviewed for efficacy in the lung cancer population received the to-be-marketed formulation.

Table 5: Number of Lung Cancer Patients per Peptide Dose

Dose of Peptide (µg)	Number of Patients
≤ 10.0	3
10.1 - 20.0	18
20.1 - 30.0	5
30.1 - 40.0	0
40.1 - 50.0	2

Data Source: appendix 16.1 (n=28)

Comment: A total of 15 patients received the old formulation. Of the 28 lung cancer patients, 2 patients received the old formulation (3-1, 3-2) and it appears that 9 other patients, though they received the new formulation, did not receive the heated dose preparation of the new formulation. One of the 28 lung patients did not have the lot number reported (4-1) [data source: Appendix 16.2.5, Vol.1.76, pg. 0302].

Correlation with Other Diagnostic Procedures:

A total of 28 of the 130 patients imaged following an injection of Technetium Tc 99m P829 had a diagnosis of confirmed or suspected lung cancer. Efficacy data were available for 26 of these 28 patients. A total of 35 confirmatory diagnostic procedures were reported by the investigators for these 26 patients. The most common diagnostic procedure identified for these patients was CT scan (24 patients, 92.3%); other procedures included biopsy/surgery (4, 15.4%) and bone scan (3, 11.5%). The correlation between Investigator read and other diagnostic test results can be found in Table 6.

Table 6: Correlation of Technetium Tc 99m P829 Images with Confirmatory Diagnostic Procedures as Reported by the Investigator (Population: Patients Valid for Efficacy Analysis with Confirmed or Suspected Lung Cancer)

Question:	Response:	All Patients (n = 26)
Do Technetium Tc 99m P829 images correlate with confirmatory diagnostic procedure?	Yes	20 (76.9%)
	No	6 (23.1%)
Do Technetium Tc 99m P829 images provide information in addition to the confirmatory diagnostic procedure?	Yes	18 (69.2%)
	No	8 (30.8%)
Do Technetium Tc 99m P829 images provide additional information regarding patient prognosis?	Yes	11 (42.3%)
	No	14 (53.8%)
	NR	1 (3.8%)
NR = Not reported		
Source: Section 14.2, Table 14.2.4, Listing 16.2.13		

Data Source: Sponsor Text Table 6, Vol. 1.76, pg. 048.

Technetium Tc 99m P829 images were reported to correlate with all diagnostic procedures in 76.9% of the patients with lung cancer. Technetium 99m P829 provided correlative or additional information to CT in all lung tumors evaluated with CT. Direct correlation with CT scans was reported in 18 cases (75.0%); in six cases the modalities did not correlate. However, in all six of the patients in which the two procedures did not correlate the investigator indicated that the Technetium Tc 99m P829 images provided additional information that the CT scan did not provide. In several of these patients, the additional information provided, as per the Sponsor, included additional sites of metastatic disease that were not detected on the CT scan. Correlation with other diagnostic procedures was reported in three of four patients (75.0%) with biopsy/surgery and in all four patients (100%) in which bone scan or MRI were the diagnostic procedures.

Overall, the investigator reported that the Technetium Tc 99m P829 images provided additional information that was not available from the confirmatory diagnostic procedure in 69.2% of the 26 patients with lung cancer; additional prognostic information was provided by the Technetium Tc 99m P829 images in 42.3% of the cases.

Comment: The results provided in this small patient population do not in any way support specific binding of the P829 peptide to somatostatin receptors expressed on lung tumors. The Sponsor enrolled patients with suspicion of having somatostatin receptor expressing tumors but did not take the extra step to confirm the presence of these receptors on the tumor by doing in vitro assays. This study was not designed to be a dose ranging study, yet, multiple peptide doses were administered at the investigator's discretion. The purpose of this practice is not known and the effects of it on efficacy was not assessed.

The Sponsor's efficacy analysis centered around the correlation of Tc99m P829 image results with other diagnostic findings. Of the 26 patients evaluable for efficacy, 20 patients had correlation between the diagnostic test and Tc99m P829 results. Of the six patients where no correlation was seen, 3 patients had a positive CT but a negative Tc99m P829 image, 3 patients had a negative CT and a positive P829 scan. Confirmation of those lesions positive on P829 but negative on CT and vice versa were not obtained by biopsy to document them as true positives.

It is also interesting to note that two patients (2-60, 2-67) in this subset had received multiple doses of Tc99m P829. There was no explanation as to the reasoning for this occurrence and it is not clear which Tc99m P829 image results were used. In looking at the variability in peptide dose and the ability of P829 to concentrate in these suspected tumors, this data does not support the selection of dose for the pivotal studies. All in all, without a standard of truth to confirm the presence or absence of disease, the results presented here are anecdotal.

One other concern regarding the amendment that added a heating step to the dose preparation. There is no discussion by the Sponsor why this step was added and if it would in anyway impact efficacy or safety. Adequate analysis of efficacy and safety should have been broken down by dose preparation method and formulation. It was assumed by this reviewer that all those patient that were dosed prior to the 12/17/1996 amendment, which added the heating step, received the unheated dose preparation.

Image Assessment: Optimal imaging time (early or late) was subjectively assessed by the investigator's. Each investigator was to assess target to non-target ratios to determine if image quality was better on early images versus the late images. Twenty eight of the 131 patient images had no optimal time reported. As per the Sponsor, the investigator's felt that the early and late images were of comparable quality in these 28 patients. A summary of the optimal imaging times for the efficacy evaluable patient (all tumor types) population and lung cancer population can be found in Table 7 and 8 respectively.

Table 7: Optimal Imaging Time
(Population: Patients Valid for Efficacy Analysis)

Optimal Imaging Time	All Patients (n = 111)
< 30 minutes	36 (32.4%)
31 to 60 minutes	25 (22.5%)
61 to 120 minutes	20 (18.0%)
> 120 minutes	2 (1.8%)
Not Reported	28 (25.2%)
Source: Section 14.2, Table 14.2.3	

Data Source: Text Table 7, Vol. 1.76, pg. 049

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Table 8. Optimal Imaging Time: Lung Cancer

Optimal Imaging Time	Lung Cancer Patients (n =26)
< 30 minutes	8 (30.8%)
31 to 60 minutes	3 (11.5%)
61 to 120 minutes	2 (7.7%)
> 120 minutes	0
Unknown	13 (50.0%)
Source: Section 14.2, Table 14.2.6	

Data Source: Table 14.2.6, Vol. 1.76, pg. 075.

Comment: The numbers for the optimal imaging times in the lung cancer population as seen in Table 8 will need to be verified by the Sponsor since the cannot be duplicated using Appendix 16.2.4, Vol. 1.77, pg. 0244. From this assessment, the optimal imaging time appears to be early post-dose. Approximately 50% of the efficacy evaluable population and 42% of the lung cancer population had optimal images between 0 and 60 minutes post-dose.

The investigator's assessment of target to non-target ratios for purposes of image quality for the efficacy evaluable population and the lung cancer population can be found in table 9.

Table 9. Assessment of Image Quality by Target to Non-Target Ratios

ASSESSMENT OF TARGET TO NON-TARGET RATIOS*	EFFICACY EVALUABLE POPULATION (N=111)	LUNG CANCER POPUALTION (N=26)
Better	26 (23.4%)	11 (42.3%)
Same	73 (65.8%)	11 (42.3%)
Less	10 (9.0%)	2 (7.7%)
Unknown	2 (1.8%)	2 (7.7%)

* The question posed to the investigators was as follows: Is the P829 image quality better, the same or less as compared to other Tc99m label Nuclear Medicine procedures used? Data Source: Tables 16.2.3 and 16.2.6, Vol. 1.76, pgs. 071 and 075.

Comment: Currently, there are not other Technetium labeled agents approved for detecting tumor in the chest and abdomen. Therefore, the results obtained from this assessment have no direct bearing on the efficacy of this drug.

Sponsor's Efficacy Conclusions: Given the current clinical development stage of Technetium Tc 99m P829 with studies focusing on patients with cancer of the lung, efficacy results from this study were reviewed for a subset of 26 patients with lung cancer. The most common diagnostic procedure identified for these patients was CT scan (24 patients, 92.3%). The efficacy results for this subset of patients were considerably better than for the overall population; Technetium Tc 99m P829 images were reported to correlate with all diagnostic procedures in 76.7% of the patients with lung cancer. Correlation with CT scans was reported in 18 cases (75.0%).

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In all six of the cases in which the two modalities did not correlate, the investigator indicated that the Technetium Tc 99m P829 images provided more information than the CT scan. In several of these patients the additional information provided included additional sites of metastatic disease that were not observed on the CT scan. Correlation with other diagnostic procedures was also high: 75.0% with biopsy/surgery (four patients) and 100% with bone scan or MRI (four patients).

Investigators were also asked to assess the optimal imaging time and the image quality of Technetium Tc 99m P829 as compared to other technetium-99m labeled nuclear medicine procedures. In the majority of cases (55.0%), the investigator judged imaging times within 60 minutes of the injection to be optimal; however, in over 25% of cases the investigator felt both early and delayed imaging times were equal in quality. The investigators rated Technetium Tc 99m P829 images as the same or better than other similar procedures in 89.2% of cases.

In conclusion, the efficacy results from this study show that Technetium Tc 99m P829 can detect somatostatin-receptor expressing tumors, and in particular has the ability to detect cancer of the lung.

Safety: All patients receiving the to-be-marketed formulation were included in the safety review.

Extent of Exposure:

Patients were to receive a single intravenous injection of Tc99m P829 as per the protocol. A total of 140 injections were administered to 130 patients. As stated earlier, 9 patients received multiple doses. For those patients receiving a single dose, the range of activity administered was 6.5-23.0 mCi and the peptide dose range was 5-50 µg (see Table 10). As per the Sponsor, 19 patient received the unheated investigational formulation and 112 received the to-be-marketed formulation. Of the 112, 34 patient received the unheated dose preparation and 78 received the heated dose preparation. The lots used for the study are as follows: Lot #9409M02A- old formulation and Lot # 9509B01B, 9609B02E, 9509B01D and 9509M01A- new formulation.

Table 10: Number of Dose Administered per Peptide Dose Range

Dose of Peptide (µg)	Number of Doses
≤ 10.0	10
10.1 - 20.0	92
20.1 - 30.0	24
30.1 - 40.0	3
40.1 - 50.0	11

Data Source: Table 14.4

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Of the 131 patients enrolled 130 patients received Tc99m P829. Of the 130, 121 patients received a single intravenous injection of Tc99m P829. Nine patients received more than one dose of Tc99m P829.

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The interval between doses for these nine patients ranged from 2-8 months. Of the 131 patients, 19 received the old formulation and 111 received the to-be-marketed formulation and 1 patient withdrew and did not receive a dose.

Sponsor's Safety Results:

Adverse Events: There were no adverse events reported during the course of this study. The Sponsor listed 2 changes in lab values as being adverse events, however. Patient 4-09 experienced an increase in lymphocyte count post injection (19%→42%) which was reported as an adverse event. Patient 4-25 experienced a drop in total protein post injection (66.3→59.9 g/L) which was also reported as an adverse event.

Laboratory Data:

Only two patients (02-17 and 02-72) were reported to have normal laboratory values pre-injection and abnormal values post-injection. At the post-injection assessment, patient number 02-17 had a sodium value below the normal range (135 mEq/L) and a triglyceride level above the normal range (205 mg/dL). For patient number 02-72 post-injection laboratory abnormalities included a low calcium (8.3 mg/dL) and a low BUN (7 mg/dL). These abnormalities were not regarded as clinically significant and were not reported as adverse events by the investigator.

Statistically significant mean changes from baseline were reported for the following parameter: increase in calcium of 0.10 mg/dL, an increase in potassium of 0.17 mEq/L, an increase in albumin of 0.06 mg/dL and a decrease in red cell distribution width of 0.52%. Neutrophil count decreased by a mean of 2.1% with a concurrent increase in mean lymphocyte count of 1.8%; mean platelet count increased 8.81×10^3 cells/mm³.

Comment: Means and median values were used to measure the central tendency of the lab data, however, they do not provide enough information when looking at safety data. The Sponsor failed to break the analyses down based on heated and non-heated versions of the dose preparation. Therefore, this information was reviewed in brief with emphasis placed on the review of the scatter plots and outliers identified for the heated dose preparation. The cut off for designation of an outlier was defined by the Sponsor as $\pm 70\%$ change from baseline. This single cut off value, which allows for excessive variability within the data, however, offers limited safety information.

In review of the scatter plots for the patients receiving the non-heated dose preparation, outliers were seen in the differential WBC counts for basophils, lymphocytes, eosinophils and monocytes. Brief review of these outliers shows most of the changes to be variable but remaining within the normal ranges for each parameter. No trends could be identified.

In review of the scatter plots for the patients receiving the heated dose preparation, outliers were seen in the following tested parameters: basophils, eosinophils, lymphocytes, monocytes, platelets, SGPT, LDH, total protein and BUN. There were 17 patients with increases in basophil levels and 5 with decreases in basophil levels. All levels, however, remained within the normal reference range.

Four patients had increases in eosinophil counts and one patient had a decrease. Again, all values remained within the normal reference range. Three patients had increases in monocyte levels with one patient having an increase above the normal reference range. No conclusions can be drawn from this data. For platelets, SGPT, LDH, total protein and BUN, outliers occurred in one patient each and no trends could be drawn from the data.

Scatter plots, by dose preparation (heated vs. non-heated), for the following parameters were not provided: Sodium, potassium, chloride, carbon dioxide, calcium, phosphorous, blood glucose, uric acid, GGT, creatinine phosphokinase and all urinalysis data.

Vital Signs:

There were no clinically relevant changes from pre-injection to any post-injection time point for any vital sign parameter. Mean changes to each time point for both systolic and diastolic blood pressure were < 1 mmHg. Mean pulse decreased from pre-injection by approximately 2 bpm at each assessment. Mean decreases of < 0.5 breaths/minute were observed for respiration and mean temperature remained virtually unchanged. The investigators judged all pre-injection vital signs to be normal in all patients assessed. Two patients (Patient Nos. 02-16 and 02-44) were reported to have abnormal vital signs post-injection; none of the changes were clinically significant. Patient No. 02-16 reported the following vital signs pre-injection: blood pressure 140/110 mmHg, pulse 76 bpm, respiration 18 breaths/minute, and temperature 98.0°F. Post-injection the only changed values were a systolic blood pressure of 144 mmHg and a pulse of 78 bpm. Patient No. 02-44 reported the following vital signs pre-injection: blood pressure 120/74 mmHg, pulse 126 bpm, respiration 32 breaths/minute, and temperature 98.2°F. The investigator reported tachycardia post-injection although the pulse was again 126 bpm, the same as observed pre-injection.

Comments: One hundred thirty patients received Tc99m P829 but 9 patients had multiple injections resulting in 140 potential safety assessments. Of the 130 patients, 19 received the old formulation, therefore, they should have performed two safety analyses, one per formulation and one per dose preparation (heated vs. Non-heated). It is not apparent from the Sponsor's results that this was done. Furthermore, 13 patients who received the new formulation, had missing vital sign assessments either at the 30 or 90 minute timepoint. From the summary statistics performed on the vital sign data found in Table 14.3.5.1, it appears that patients with the old formulation and patients with missing data were not excluded from the safety analysis. The sample population numbers do not appear correct based on the patients with missing data and patients receiving the old formulation. It was also found that all patients (n=31) at site 4 did not have their respiration rate monitored.

Summary statistics were performed but mean and median values are not sufficient. A brief look at the line listings show minimal changes in vital sign data. The two cases that the Sponsor deemed abnormal as listed above do not make sense to this reviewer. There were other patients who had greater changes in blood pressure and pulse than that cited above for patient 2-16 but were not reported as abnormal.

Normal reference ranges for the vital sign assessments were not provided so there is no way of knowing how the Sponsor reviewed this data.

Local Response:

An abnormal local response was reported in one patient (02-44) at both the 30 and 90 minute post-injection time point. The type of response was not reported by the investigator. This patient was subsequently re-dosed (patient's new assignment 02-66) and the dose was tolerated well.

Sponsor's Safety Conclusions

Technetium Tc 99m P829 administered as a single intravenous injection to patients with a clinical diagnosis of cancer was safe and well tolerated. Repeat administration in nine individuals was also well tolerated. No serious adverse events were reported during this study and none of the patients discontinued the study due to adverse events. Treatment-emergent adverse events were reported in two (1.5%) of the 130 patients. Both events were considered mild in intensity and probably unrelated to the study agent by the investigator; no treatment was required for either event.

There were no clinically significant abnormalities detected by the assessment of hematology, clinical chemistry or urinalysis laboratory parameters and no clinically significant changes were observed in vital signs.

Sponsor's Overall Conclusions: In conclusion, Technetium Tc 99m P829 administered as a single intravenous injection to patients with a clinical diagnosis of cancer was safe and well tolerated. Technetium Tc 99m P829 can detect somatostatin receptor-expressing tumors and in particular has the ability to detect cancer of the lung. The agent appears to provide additional information to the clinician that is not obtained with other currently available diagnostic procedures. In 80 to 92 percent of the cases Technetium Tc 99m P829 either correlated with or provided additional information when compared to the standard diagnostic method.

Reviewer's Discussion:**Design:**

Given the objective for this study-To detect and localize tumors known or expected to express somatostatin receptors, the design of this study does not appear to be adequate. The design of this study, in no way confirms the presence of somatostatin receptors on any of the tumors studied, therefore, any conclusions of P829 specifically binding to a somatostatin receptors on the tumor surface cannot be made. The only potential conclusion that could be made is that this agent may or may not bind to tumor. The specific mechanism of binding cannot be commented upon.

If it was the intention to draw the conclusion of a specific binding claim of P829 to somatostatin receptors, then this would require tissue procurement with in vitro assay testing for confirmation of the presence or absence of the receptors.

Realizing that this study is Phase 2 and hypothesis generating, the presence of a standard of truth was not essential.

However, the information gained by confirming the truth between the discrepancies seen between P829 image results and other diagnostic tests could have had dramatic influence on the design for a Phase 3 study. The Sponsor should have pursued those patients where discrepancies were identified so that adequate follow-up could have been employed to confirm the presence or absence of disease to explain the discrepancies.

The application of two formulations and two different dose preparation processes (heated vs. non-heated) should have been addressed as part of the statistical and efficacy analyses plans for this study. The introduction of these variables and the lack of analysis as to their influence on the endpoints of this study (both efficacy and safety) has led to the lack of interpretable results.

The rationale for the use of multiple peptide doses in this clinical trial is not adequately identified. This trial was not designed as a dose ranging trial, however, the investigators were allowed to adjust the peptide dose at their discretion. The influence of the different peptide doses on efficacy and safety was not assessed.

Efficacy:

Given the tumor specific indication proposed by the Sponsor for the NDA, only those patients enrolled with lung tumors were reviewed for purposes of efficacy.

Of the 26 evaluable patients with lung cancer, 20 patients had correlation between the diagnostic test and Tc99m P829 results. Of the six patients where no correlation was seen, 3 patients had a positive CT but a negative Tc99m P829 image and 3 patients had a negative CT and a positive P829 scan. Confirmation of those lesions positive on P829 but negative on CT and vice versa were not obtained by biopsy or other type of diagnostic follow-up. The information gained from follow-up would have been beneficial in interpreting the potential efficacy of this agent so that an adequate Phase 3 trial could be designed. The results of the questions posed to the investigator's, regarding additional information obtained by the Tc99m P829 image study, cannot be assessed given that the actual nature of the information obtained was not specified.

The information gained by the investigator's imaging time assessment identified early imaging (up to 60 minutes post-dose) to be optimal. The information gained with regards to target to non-target ratios assessments does not appear to have any bearing on the efficacy analysis since there are currently no approved Technetium labeled agents for imaging tumor in the chest and abdomen.

The issue of multiple peptide dosing in this study was addressed above in the design discussion but plays an important role in the efficacy assessment. The lack of a standard peptide dose makes it difficult for efficacy to be assessed. Because so many peptide doses were utilized, breaking the population into subsets based on peptide dose is difficult for the 26 patients with lung tumor.

The subsets are too small to draw any useful information. Only two patients with lung cancer received the 50 µg peptide dose that was used in the pivotal trials.

Phase 2
Study P829-23