

6.2 Phase 1

6.2.1 Study P829-12

Phase 1, P829-12 (Volumes 1.31-1.33)**Study Period:** October 29, 1997 to February 17, 1998)**Formulation:** Heated, Market Formulation**Population:** Healthy subjects and patients with renal and hepatic dysfunction or neoplasm.**Title:** A Single-Center Clinical Study to Evaluate the Pharmacokinetics, Radiation Dosimetry and Safety of Tc99m P829 in Normal Volunteers and Patients.**Objectives:**

- 1) To evaluate the safety of Technetium Tc 99m P829 in normal volunteers and patients displaying evidence of renal or hepatic functional impairment, or having neoplastic disease.
- 2) To evaluate the pharmacokinetics and radiation dosimetry of Technetium Tc 99m P829 in these subjects. Pharmacokinetic parameters to be evaluated included distribution, metabolism, and excretion.
- 3) To evaluate the pharmacokinetics of unlabeled P829 (i.e. the immunoreactive core peptide) in these subjects.

Design: This is a Phase 1 single center, open-label trial to evaluate the biodistribution, metabolism, elimination and safety of Tc99m P829 in normal healthy volunteers and patients with renal or hepatic dysfunction or patients with neoplasm. Up to 30 patients were to be enrolled including 12 normals (6 male and 6 female), 6 patients with mild to moderate renal dysfunction, 6 patients with lung cancer, 6 patients with Neuroendocrine tumors and 6 patients with hepatic dysfunction. All subjects/patients were to receive a single intravenous administration of 15-20mCi of Tc99m P829 (50µg of peptide). Following drug administration, Whole body anterior and posterior imaging was to be performed. Blood samples were to be collected at multiple time points post-injection. Urine was to be collected for 24 hours post-injection for monitoring renal clearance. Human dosimetry was to be calculated utilizing the Medical Internal Radiation Dose (MIRD) Schema. Safety was to be assessed by monitoring adverse events, vital signs and clinical laboratory tests and immunogenicity testing. No measures of efficacy were to be performed. Table 1 summarizes the timing of all events.

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Table 1.
Flow Chart for Pharmacokinetic, Biodistribution, Immunogenicity, and Safety Assessments

Time	Assessment						
	Blood Sample for PK Analysis	Vital Signs	Hematology, Blood Chemistry & Urinalysis	Urine for PK Analysis	Whole Body Imaging	Feces	Immunogenicity Testing
-24 hr to 0			X				
-5 hr to 0	X	X					X
3 min	X						
5 min	X	X					
7 min	X						
10 min	X				X		
15 min	X						
30 min	X	X					
1 hr	X	X		X	X		
2 hr	X			X	X		
3 hr		X		X			
4 hr	X		X	X	X		
8 hr	X			X			
12 hr	X			X			
24 hr	X	X	X	X	X		
24-36 hr						X	
3 weeks							X*

Note: Time 0 represents the time of administration of Technetium Tc 99m 0829.
 * To be collected from 10 normal subjects.

Data Source: Sponsors In-Text Table 9-A

Results:

Protocol Deviations:

- 1.) Several failures to collect individual subject/patient safety data were reported.
- 2.) No fecal samples were collected.
- 3.) No 12 hour blood samples for PK analysis were collected.
- 4.) Laboratory tests were performed at 4 hours instead of 3 hours post-injection.

Dose: A single intravenous administration of 15-20 mCi of Tc99m P829 (50µg) was administered. The heated dose preparation of the to-be marketed formulation was used. Lot numbers used in this study are the following: 9609B02F and 9609B02G.

Disposition:

23 subjects were enrolled. Of those enrolled, 19 subjects completed the study, 3 subjects did not complete safety and 1 subject did not complete Tc99m P829 imaging or safety. There were no withdrawals by subjects from this study.

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Demographics: Please see Table 2.

Table 2. Demographics

PARAMETER	TOTALS
GENDER	
Male	14 (61%)
Female	9 (39%)
AGE (yrs)	
mean	34.6
min	19
max	67
WEIGHT (kgs)	
mean	75.4
min	52.6
max	118.8
HEIGHT (cm)	
mean	170.9
min	142.2
max	188.0
RACE	
Caucasian	12
Black	10
Asian	1

Data Source: Section 14, Table 2.1

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Of the 23 subjects/patients enrolled, 12 were normal, 5 had hepatic dysfunction, 4 had renal dysfunction and 2 had lung cancer.

Sponsor's Pharmacokinetics Results:

Plasma radioactivity levels after Technetium Tc 99m P829 administration exhibited triphasic decay, with a rapid decline in radioactivity soon after administration (mean half-life of 4.4 min), followed by a more gradual decline with a half-life of 48.7 min, and a slow decline with a half-life of 19.8 h (mean values). Plasma radioactivity data were fit using a three-compartment pharmacokinetic model. Overall, systemic clearance (CL) was 155 mL/min and renal clearance (CL_R) was 22.8 mL/min. The low renal clearance, relative to systemic clearance, indicates that P829 undergoes extra-renal elimination. Volume of distribution (V_{ss}) was large (114 L) and exceeded total body water volume. Mean plasma protein binding was low (12.1%). Pharmacokinetics of P829 in renally or hepatically-impaired subjects, or in patients with lung cancer, were not appreciably different from those in healthy subjects (see Table 3). Statistical analysis did not indicate any consistent effects of age and weight on pharmacokinetic parameters. However, a statistically significant gender effect on clearance was observed, with female subjects having a lower CL (mean value of 96.5 mL/min compared to 195 mL/min in males).

Table 3. Summary of Pharmacokinetic Parameters of Plasma Total Radioactivity Concentrations

Subject/Patients		Pharmacokinetic Parameter		
		CL (mL/min)	V _{ss} (L)	t _{1/2} (h)
Healthy	n	9	9	9
	Mean	155	106	22.4
Hepatic dysfunction	n	3	3	3
	Mean	204	142	18.0
Renal dysfunction	n	3	3	3
	Mean	130	143	17.2
Lung cancer	n	2	2	2
	Mean	115	60.0	14.8

Data Source: Text Table 11-A, Vol. 1.31, pg. 043.

Sponsor's Biodistribution Results:

Ten minutes post-injection, distribution of total radioactivity was greatest in the abdomen (59%). However, in terms of individual organs, the highest activities were in the liver and kidneys (7% to 15%) and lowest in the thyroid (0.4%). Radioactivity in most tissues (including lung tumor) accounted for approximately 1% to 3% of the administered dose. During the 24 hours post-injection, activity remained nearly constant in these regions. Tissue distribution of P829 in renally or hepatically-impaired patients, or in patients with lung cancer, was not appreciably different from those in healthy subjects.

Safety:

Deaths: 0

Withdrawals due to an Adverse Event: 0

Serious Adverse Events: 0

Severe Adverse Events: 0

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Extent of Exposure: The Tc99m dose administered ranged from 8.2 to 15.3 mCi. Only doses with $\geq 90\%$ of radiochemical purity were administered. The actual peptide doses administered were not reported. Lots used in this study were 9609B02F and 9609B02G.

Adverse Events: Two adverse events were reported in two subjects. Both events were not considered to be related to the study drug. No deaths or serious adverse events were reported.

One healthy volunteer experienced diarrhea beginning approximately 9.5 hours post-administration. The subjects symptoms were mild and intermittent and resolved without treatment on the following day.

One healthy volunteer experienced an eye abnormality which was not further defined by the Sponsor. The onset of the event was not identified but was considered moderate in severity. The event resolved after treatment administration, however, type of treatment was not specified.

Laboratory data(Chemistry and Hematology): No specific trends were seen in the data reported.

Urinalysis data: No trends were seen in the data.

Vital Sign Data: No specific trend identified in the data.

Immunogenicity data: Nine normal subjects did not show the presence of IgG or IgM antibodies at 3 weeks post-drug administration.

Sponsors Conclusions:

- P829 was characterized a drug of low protein binding, low systemic clearance and large volume of distribution and a terminal half-life of 20 h. Pharmacokinetics of P829 in renally or hepatically-impaired patients, or in patients with lung cancer, were not appreciably different from those in healthy subjects. There appeared to be a sex-related difference in the systemic clearance of P829.
- Distribution of total radioactivity was greatest in the liver and kidneys and in most tissues accounted for approximately 1% to 3% of the administered dose. Distribution of P829 to tissues was similar in healthy subjects and in patients with renal dysfunction, hepatic impairment or lung cancer.
- There was no generation of P829-specific antibodies.

Reviewer's Discussion:

This study was designed to study the pharmacokinetics and dynamics of Tc99m P892 in both normal healthy volunteers and patients with renal or hepatic dysfunction, or neoplasm. Elimination was found to be mainly other than renal, however, the actual route of elimination was not identified. The lack of feces collection resulted in failure to identify the major route of elimination and to determine if metabolism of this drug exists. Plasma radioactivity levels exhibited triphasic decay exhibiting a rapid decline, followed by a more gradual decline followed by a slow decline. Mean half-lives are as follows for each phase respectively: 4.4 minutes, 48.7 minutes and 19.8 hours. Please see Biopharm review for detailed analysis of study design and results.

The safety analysis was performed on both healthy volunteers and patients using the heated dose preparation of the to-be-marketed formulation. Those patients studied included renally impaired, hepatically impaired and lung tumor patients. The sample sizes for these three subgroups was small making any accurate statement of safety in these three groups premature. Pertinent baseline laboratory values for both the renally and hepatically impaired patients are listed in Tables 4 and 5. The Sponsor did not provide the criteria used to enroll these types of patients, therefore, from the lab values seen at baseline, it does not appear as though severe disease states were studied. There are a few patients with significant abnormal values, however, there are more patients with very limited laboratory abnormalities.

The small sample sizes and the limited spectrum of disease states studied make it difficult to make a general statement of the drugs safety in these patient subpopulations.

Table 4. Baseline labs for Patients with Hepatic Dysfunction

Patient	Medical History	AST U/L	ALT U/L	Alk Phos U/L	GGT U/L	LDH U/L	t Bili mg/DL	Triglyceride mg/DL
13	History of Sarcoidosis	28	48↑	70	37	490	0.5	249↑
15	No liver disease noted	22	44	65	16	419	0.2	131
16	Remote history of Alcohol Abuse	27	39	79	35	459	0.3	155↑
17	Gunshot to posterior liver, alcohol abuse	68↑	74↑	66	247↑	842↑	0.6	204↑
18	History of elevated AST and ALT	42↑	58↑	80	47	352	0.6	41

Data Source: Appendix 16.2.3-Patient Data Listing 2.2, Appendix 16.2.8-Patient Data Listing 3.3, ↑= lab value elevate above normal range.

Table 5. Baseline Labs for Patients with Renal Dysfunction

Patient	Medical History	Cr mg/DL	BUN mg/DL
10	Mild HTN	0.9	10
19	CHF, HTN	4.9↑	68↑
20	CRF	3↑	19
22	Labile HTN	1.4↑	38↑

Data Source: Appendix 16.2.3-Patient Data Listing 2.2, Appendix 16.2.8-Patient Data Listing 3.3, HTN = hypertension, CHF = congestive heart failure, ↑= lab value elevated above normal range.

Overall, no overt trends were seen in the laboratory data and vital sign data collected. Immunogenicity testing, which was only performed in the normal subgroup, was negative for the presence of IgG and IgM antibodies to the P829 peptide.

Two adverse events were reported in two healthy volunteers. The onset of the adverse event, diarrhea, was not suggestive of test drug causality. The other adverse event, eye abnormality, was not discussed in detail by the Sponsor making it difficult to assess its relationship to the test drug. Type of eye abnormality, its time of onset and the type of treatment given are questions that need to be addressed by the Sponsor in order to make any judgments regarding causality.

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Reviewer's Conclusions:

- 1.) The study did not adequately identify the major route of elimination and the presence of or absence of drug metabolism. Understanding of this information is necessary for the design of future studies.
- 2.) The significance of the gender effect seen on clearance is not known and should be adequately studied.
- 3.) Given the limited sample size, the test drug appears to be safe.
- 4.) No statement can be made at this time regarding the safety of Tc99m P829 or lack there of, in hepatically or renally impaired patients.

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PHASE 1
STUDY P829-13

6.2.2 Study P829-13

Phase 1, P829-13 (volume 1.34)

Study Period: December 4, 1997 to December 12, 1997

Formulation: Market Formulation

Population: Healthy volunteers

Title: A Single-Center Clinical Study to Evaluate the Pharmacodynamics of P829 in Normal Human Volunteers.

Rationale: P829 is a somatostatin analog developed for use in diagnostic imaging of somatostatin-receptor bearing tumors. Octreotide, another somatostatin analog, has been found to exhibit somatostatin-like activity that can interfere with the insulin response to a glucose load. It is of interest to the Sponsor, as a matter of safety, to establish how P829 will affect the normal physiologic response to a glucose challenge.

Objectives:

- 1.) To study the pharmacodynamic effects of P829 and Octreotide on the glucose tolerance response in normal volunteers, and
- 2.) To study the potential generation of antibodies to P829 in normal volunteers following *in vivo* exposure to clinical doses of P829.

Design: This is a single center open-label Phase 1 study to evaluate the effects of unlabelled P829 on antibody production and on glucose tolerance testing. Approximately 9 normal subjects will be enrolled in the study for a duration of 8 days. On days 0, 4 and 8, each subject will receive one of the following doses: 50 µg of P829 peptide, 50 µg of Octreotide or no dose administration. Approximately 5 minutes after dosing, each patient will undergo a glucose tolerance test (GTT). The evening of days -1, 3 and 7 will be the start of the 12 hour fasting period just prior to dosing. Days 1, 2, 5 and 6 will act as washout days. After administration of glucose challenge, blood will be collected at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours post administration. Safety monitoring will include the monitoring of vital signs, clinical laboratory tests and adverse events. Immunogenicity testing will be performed on blood samples taken 3 weeks post P829 administration. Descriptive statistics of the difference in Glucose Tolerance Test response for both P829 and Octreotide curves will be compared to baseline. Statistical comparisons between baseline and post-injection glucose tolerance response will be analyzed.

Comment: *Octreotide is an approved therapeutic drug. The minimum dose is 50 µg. The Sponsor does not give a rationale for comparing a diagnostic drug (Tc99m P829) to a therapeutic drug, however, it is anticipated by this reviewer, that since the P829 dose used is within the same peptide range as the therapeutic drug, Octreotide, it would be beneficial, for safety purposes, to establish if P829 has any affect on glucose metabolism.*

Results:

No Protocol deviations were reported.

Disposition: A total of 9 subjects were enrolled. All subjects completed the study and were included in the pharmacodynamic analysis and evaluated for safety.

Demographics: See table 1 below.

Table 1. Demographics

Parameter	Statistic
Gender	
Male	5
Female	4
Age (yrs)	
Mean	41.8
Range	21-69
Weight (kgs)	
Mean	81.3
Range	58.0-105.2
Height (cm)	
Mean	172.5
Range	152.6-190.0
Race	
Caucasian	9

Data Source: Appendix 16.2.1, Listing 1.0

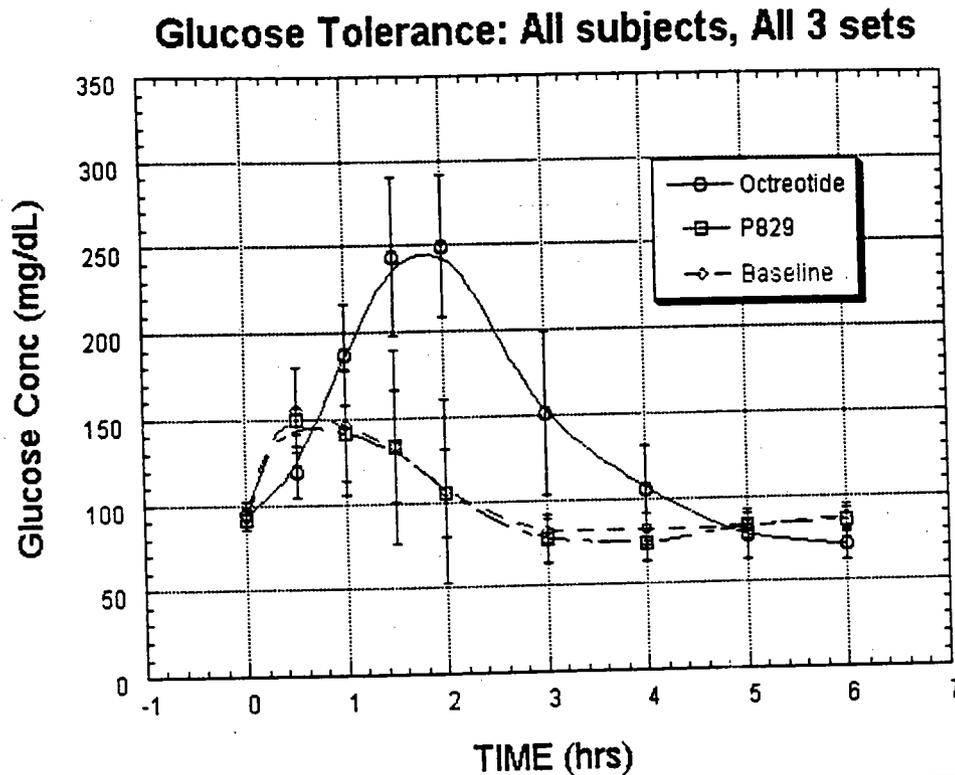
Pharmacodynamic Results: As per Sponsor

Glucose tolerance curves show that the GTT response with P829 treatment was similar to baseline (no peptide). A minimal and transient rise in serum glucose levels within 1 hour post administration of the glucose tolerance beverage occurred with both P829 and baseline (no peptide). Figure 1.0 also shows that, with Octreotide treatment, a large and more prolonged rise in serum glucose levels occurred within 1 to 2.5 hours post administration of the glucose tolerance beverage, compared to the GTT baseline response (no peptide) or the GTT response with P829 administration.

Mean serum glucose levels increased from baseline (time 0 minutes) for all 3 treatments. For P829 or no peptide treatment, there was a transient increase in mean serum glucose levels, which returned to baseline 2 hours post administration of the glucose tolerance beverage. With Octreotide treatment there was a more sustained increase in mean serum glucose levels which returned to baseline 4 hours post administration of the glucose tolerance beverage.

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Figure 1.0 Glucose Tolerance: All subjects, Baseline, P829 and Octreotide



Data Source: Figure 1, Vol. 1.34, pg. 066.

Immunogenicity Testing: No P829 specific IgG or IgM antibodies were identified at 3 weeks post administration of unlabelled P829.

Safety:

Deaths: 0

Withdrawals due to an Adverse Event: 0

Serious Adverse Events: 0

Severe Adverse Events: 0

Extent of Exposure: The heated dose preparation of the to-be-marketed formulation was used. The Lot number used was 9609B02G. No activity dose was administered. Actual peptide doses were not reported in the data listings but the protocol called for 50 µg of P829 peptide to be administered.

Adverse events:

Seven out of 9 subjects reported a total of 25 treatment emergent adverse events, all of which were mild. Five subjects experienced a total of 6 adverse events following P829 treatment, all of which were "possibly related" to P829 treatment. Six subjects experienced a total of 13 adverse events following Octreotide treatment, 10 of which were "possibly related" to Octreotide treatment.

Three subjects experienced a total of six adverse events following no peptide treatment (glucose tolerance beverage only), all of which were "unrelated".

Table 2. Adverse Events

N=9	50 µg P829	50 µg Octreotide	No Peptide	Total
Number of subjects with AE	5	6	3	7
Body As Whole	1 (11%)	3 (33%)	1 (11%)	4 (44%)
Asthenia	0	0	1	1
Fatigue	1	3	1	4
CNS & PNS	2 (22%)	3 (33%)	2 (22%)	6 (67%)
Dizziness	1	1	0	2
Headache	2	2	2	5
Gastrointestinal	1 (11%)	5 (56%)	1 (11%)	5 (56%)
Abdominal Pain	0	1	0	1
Nausea	1	4	1	4
Psychiatric	1 (11%)	0	1 (11%)	2 (22%)
Somnolence	1	0	1	2
Vascular	0	2 (22%)	0	2 (22%)
Flushing	0	2	0	2

Data Source: Section 14, Table 5.0

Comment: All patient received oral glucose 5 minutes post drug administration. Affect of an oral glucose load on patients is another variable which must be considered when trying to assign causality to the production of an adverse event. Of the adverse events seen post P829 administration, the onset of one adverse event occurred within the first half hour post P829 administration. This event was nausea. Nausea also occurred in the control group (no peptide) within 30 minutes as well. Fatigue, headache and somnolence was seen in the control group as well.

Clinical Laboratory Data:

No consistent treatment emergent changes were observed.

Comment: Since only two blood samples were drawn, one at baseline and one on day 8, the last day of the study, assigning causality to any abnormal lab value could not be accurately done due to the multiple treatment variables administered between assessments (i.e. P829, Octreotide and Glucose administration). No significant changes in laboratory values were seen, however.

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Vital Signs:

The review of individual subject data revealed that 7 subjects had clinically significant changes in pulse rate according to the criteria designated in the protocol (range 24 to 40 bpm) and one subject had a clinically significant change in SBP according to the protocol (subject 829-13-01-03 had a SBP of 148 mmHg 30 minutes prior to discharge compared to a SBP of 110 mmHg at baseline prior to no peptide treatment). The investigator did not consider the above changes in pulse rate and SBP to be clinically significant.

Comment: All mean vital sign values at 30 minutes prior to discharge compared to baseline showed higher mean values. This observation was seen for each test assessment (i.e. Post P829, Post-Octreotide and post- no peptide)

Sponsor's Conclusions:

In normal healthy volunteer subjects:

- P829 did not alter the physiological response to a glucose challenge.
- P829 did not lead to the generation of P829 specific antibodies.
- A single IV injection of P829 was safe and well tolerated.
- Octreotide did alter the physiological response to a glucose challenge.

Reviewer's Discussion:

The Sponsor's rationale for doing this clinical study was to assess whether P829, a somatostatin analog, exhibits some somatostatin-like activity and thus influences the insulin response to a glucose load (glucose tolerance test). All subjects in this study had 3 glucose tolerance tests performed, one each following P829 administration, Octreotide administration and no drug administration (control). In most cases, the glucose response seen post-P829 mimicked that seen for the post-control (no peptide dose) group. The glucose response seen post-Octreotide administration exhibited a larger and more prolonged rise in serum glucose in response to the oral glucose load as compared to the control response. This prolonged rise seen post-Octreotide, however, did subsequently drop to more appropriate levels by the 5-6 hour assessment. Octreotide is an approved therapeutic agent for the treatment of symptoms related to carcinoid tumors and Vasoactive Intestinal peptide tumors. The therapeutic dose starts at 50µg of peptide. It is anticipated by this reviewer, that since the P829 dose used is within the same peptide range as the therapeutic drug, Octreotide, it would be beneficial to establish that P829 does not influence glucose metabolism, which may be seen with Octreotide therapy. The current approved diagnostic somatostatin analog, Octreoscan, has an approved peptide dose of 10µg.

These results shown by the Sponsor reveal the lack of any significant trends in glucose response after P829 administration in this small sample size of 9 healthy volunteers. Due to this small sample size, a generalized statement of P829's lack of effect on the insulin response to glucose loading cannot be made, however, the design of this study which uses the patient as their own control offers more credence to the results.

Safety data was difficult to assess and assign causal relationship due to the multiple treatment variables which were introduced between the laboratory assessments. Laboratory data were collected at baseline and at the end of the study (day 8). Over the course of these 8 study days, subjects received P829, Octreotide and glucose, all of which could have influenced the safety profile of this study. The lack of assessments between administrations makes it difficult to attribute causality. Overall, when looking at the laboratory data and vital sign data, however, no specific trends were seen in the data to suggest a safety problem that would warrant further directed study. Six adverse events were reported after P829 administration, 13 following Octreotide administration and 6 following no drug administration. The adverse event profile seen post-P829 was similar to that seen post-control (no dose). Immunogenicity test performed at 3 weeks post peptide dosing did not show the presence of IgG or IgM antibodies.

Reviewer's Conclusions:

- 1.) No abnormal trends in glucose serum levels were seen post-P829 administration in this small sample size of healthy volunteers.
- 2.) A consistent rise in serum glucose levels was seen post-Octreotide administration with values leveling off by the end of the study period. Note: Octreotide is a therapeutic drug, not a diagnostic drug. The Sponsor did not compare P829 to the approved diagnostic drug, Octreoscan™ (peptide dose approved is 10µg).
- 3.) No trends in the safety data were identified post-P829 administration.

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PHASE 2
STUDY P829-30II/a

6.3 Phase 2

6.3.1 Study P829-30/IIa

Phase 2, P829-30/IIa (Volume 1.38)

Study Period: December 19, 1996 to September 5, 1997.

Formulation: [redacted] Market Formulation

Population: Patients with non-small cell lung cancer

Foreign Study: Belgium

Title: A limited Phase 2, open label, study to determine the efficacy of P829 in the scintigraphic localization of primary tumor and metastatic spread, especially to the mediastinum, of non-small cell cancer of the lungs.

Objectives: The study aims at establishing the feasibility of scintigraphy with technetium labeled P829 in non-small cell cancer of the lungs. This will involve the visualization of both primary and metastatic sites, especially in the mediastinum. In addition, optimal scintigraphic imaging time will be assessed.

Design: This is an open label, Phase 2 study to determine the feasibility of Tc99m P829 in detecting non-small cell lung cancer. A minimum of 10 patients presenting with lung cancer and an FDG-PET scan will be enrolled. All patients will be 18 years or older, sign informed consent and will have histologic proof of non-small cell lung cancer. All patients will have both FDG-PET and Tc99m P829 scintigraphy performed. An intravenous dose, [redacted] of 19.5 mCi of Tc99m P829 will be administered followed by Planar and SPECT imaging. Planar imaging will begin at 10 minutes post-dose and will be repeated again between 2-4 hours post-dose. SPECT imaging will be performed between 2-4 hours post-dose. The primary efficacy endpoint will be the comparison of Tc99m P829 tumor localization to the localization results of radiologic examination and FDG-PET scintigraphy. In addition, optimal imaging time will be assessed. Safety will include monitoring for adverse events.

Population: At least 10 patients over 18 years of age will be recruited from patients presenting to the department of Nuclear Medicine at the University Hospital of Liege for the evaluation of their lung cancer by FDG-PET. All patients will have histologic proof of non small cell lung cancer and sign an informed consent. Those patients known to be pregnant or those with recent minor or major thoracic surgery will be excluded.

Dose: Patients will receive an intravenous dose of Tc99m P829. The dose will contain 50µg of peptide and 720 MBq (19.5 mCi) of activity.

Imaging: Scintigraphy will start approximately 10 minutes and 2 and 4 hours post-administration. Scintigraphy will involve at least one SPECT acquisition over the thorax. Planar images will also be obtained.

Efficacy: At entry into the study, the results of all relevant radiological procedures and histologic examinations done previously will be recorded on the CRF. The location of the tumor found by scintigraphy will be compared to the localization reported from the standard radiological examinations and from the FDG-PET. In addition, the optimal time for imaging will be assessed.

Safety: Patients will be monitored for adverse events for a period of 3-5 hours after the administration of test drug. Vital sign and laboratory data will not be collected.

Statistical Analyses: No analysis plan was identified

No amendments were made to the protocol.

Study Results:

Protocol Deviations:

- Histologic proof of non-small cell cancer was not obtained (patient 7).
- Patients 2, 12 and 13 were administered slightly more (1.1 mCi, 0.5 mCi, and 2.5 mCi, respectively) than the protocol-specified maximum dose of 19.5 mCi technetium-99m.

Disposition: Thirteen patients were enrolled. All patients completed the study. Twelve patients were included in the efficacy analysis.

Demographics: Of the 13 patients enrolled, 3 were female and 10 were male. The average age was 61.7 years. Two patients had prior history of lung cancer and treatment (patient 7 and 11). Patient 7 had a left pneumonectomy in 1992. Patient 11 had radiation treatment for brain metastases and chemotherapy, as well as, a right superior lobectomy (1991). Patient 5 presented with inoperable lung cancer and had 3 courses of chemotherapy prior to the Tc99m P829 and FDG-PET. One patient (13) had recent chemotherapy on 8/22/97 (FDG-PET performed 8/22/97 and Tc99m P829 performed 9/5/97).

Comment: No other demographic parameters were collected.

Presence of non-small cell cancer was classified as "certain" based on biopsy in nine patients, "certain" based on sputum or bronchial washing in one patient, "probable" based on biopsy in two patients, and "suspected", but not proven, in one patient. Diagnostic techniques used to determine TNM classification at entry were the following: X-ray of thorax, CT of thorax, Bone scan, and CT of the abdomen. X-ray and CT of the thorax were required in all patients while Bone scan and CT of the abdomen were acquired in 10 patients.

Table 1. Location and Histological Presentation of Primary Tumor

Patient Number	Cancer Present	Primary Tumor Location	Type of Histological Proof	Histological Type	TNM Classification
1	Certain	LUL	Biopsy	Large Cell	T3-N3-M0
2	Probable	RML	Biopsy	Adenocarcinoma	T3-N3-M0
3	Probable	RUL	Biopsy	Squamous	T2-N2-M0
4	Certain	LLL	Biopsy	Squamous	T4-N3-M0
5	Certain	RML	Sputum or bronchial washing	Adenocarcinoma	T4-N1-M0
6	Certain	RLL	Biopsy	Squamous Cell	T4-N0-M1
7	Suspected		not obtained	NA	
8	Certain	LLL	Biopsy	Squamous Cell	T2-N1-M1
9	Certain	RML	Biopsy	Adenocarcinoma	T3-N3-M0
10	Certain	RLL	Biopsy	Squamous Cell	T2-N0-M0
11	Certain	RUL	Biopsy	Adenocarcinoma	T2-N0-M0
12	Certain	LUL	Biopsy	Squamous Cell	T2-N0-M0
13	Certain	LLL	Biopsy	Adenocarcinoma	T2-N2-M0

Data Source: Appendix 16.2 Table 3, 6

The timing between P829 imaging and PET imaging is listed below for all patients. The time ranged from 1-18s day, with a median of 3 days. In all cases, the FDG-PET study was performed prior to the Tc99m P829 study. Early planar images were acquired in all patients from 1 to 2 hours. Planar images and SPECT images were acquired from 3 to 5.5 hours post-administration. SPECT was the final acquisition modality in all 13 patients. Lesion/background ratios were graded as either low, moderate or high. Lesion/background ratios were moderate to high for all 13 SPECT studies done at 3 to 5.5 hours, but only for 16 of 26 planar studies. The only false positive lesion was on planar images at 1 hour. For all 13 patients the lesion/background ratio on the SPECT study was better than that for the early planar images. In the opinion of the investigator, the optimum time for imaging following administration of technetium Tc 99m P829 in this 13-patient study ranged from 1 to 5.5 hours. The majority of images considered optimum were acquired between 3 to 5 hours post-injection.

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Table 2. Time between Scintigraphy

Patient Number	Days between PET And Tc99m P829 Imaging
1	6
2	1
3	13
4	3
5	2
6	18
7	7
8	3
9	3
10	1
11	2
12	2
13	14

Data Source: Appendix 16.2 Table2

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Comment: The time between FDG-PET and Tc99m P829 imaging suggests that comparability of the clinical state per patient was captured.

Efficacy:

The protocol was modified to include tumor staging using the TNM classification of the American Joint Committee on Cancer staging (Please see Appendix A for the staging criteria). The Sponsor does not identify any amendments to this protocol, therefore, this was a post hoc addition to the analysis plan.

The primary indicator of efficacy was the patient-based rate of agreement between Technetium Tc 99m P829 results and histopathology. Because all evaluable patients had histologic proof of non-small cell lung cancer, visualization of any lesion in the thorax by Tc99m P829 was considered agreement by the Sponsor. One or more lesions were detected by Tc99m P829 in all patients who had histologic proof of non-small cell lung cancer (agreement rate = 100%).

Comment: No lesion-based rate of agreement between Tc99m P829 and histopathology was obtained in this study.

A secondary indicator of efficacy was the comparison of the number of lesions identified by FDG-PET and Tc99m P829. The results of this analysis can be found in Table 3.

Table 3. Lesion Identification per Modality

Patient Number	Number of Lesions	Number of Lesions seen on both Modalities	Number of Lesions seen on FDG-PET alone	Number of Lesions seen on Tc99m P829 alone
1	9	9	N/A	N/A
2	5	4	1	N/A
3	4	4	N/A	N/A
4	4	3	1	N/A
5	1	1	N/A	N/A
6	8	5	1	2
7*	2	1	N/A	1
8	1	1	N/A	N/A
9	6	6	N/A	N/A
10	6	4	1	1
11	4	4	N/A	N/A
12	1	1	N/A	N/A
13	3	1	N/A	2
TOTAL	54	44	4	6

*Patient 7 did not have histopathologic diagnosis. N/A= Not applicable, Data Source: Appendix 16.2 Table 12, Vol. 1.38, pg. 0110.

Other secondary indicators of efficacy were patient-based rates of agreement between the TNM classification and Technetium Tc 99m P829 results, lesion-based agreement between radiologic evidence and Technetium Tc 99m P829 results and lesion-based agreement between Technetium Tc 99m P829 results and FDG-PET results.

For detection of regional lymph node lesions and metastatic lesions, FDG-PET and Technetium Tc 99m P829 "N" classification and "M" classification were identical to each other for ten of twelve patients (83%). Results of the two methods were different for Patient 6 and Patient 13. With Patient 6, the Technetium Tc 99m P829 identified a contralateral lesion that was not identified by FDG-PET scan, resulting in a different "N" classification for the two methods. With Patient 13, a lymph node lesion was detected in the Technetium Tc 99m P829 images but not in the FDG-PET scan, again resulting in different "N" classifications using the two methods. The Technetium Tc 99m P829 results agreed with histopathology and the TNM classification for this patient on entry to the study.

Comparison of TNM classification based on Technetium Tc 99m P829 results with TNM classification on entry to the study indicated that the TNM classification would have been changed for 6 patients if they were based on Technetium Tc 99m P829 scintigraphy. However, patient management did not change due to Technetium Tc 99m P829 results or the FDG-PET results.

Table 4. TNM Classification

Patient Number	TNM Classification before Study	TNM Classification after FDG-PET	TNM Classification after Tc99m P829	TNM Classification Comments	Follow-up Information Available
1	T3-N3-M0	TX*-N3-M1	TX-N3-M1	M1= Pleura metastasis	None
2	T3-N3-M0	TX-N3-M0	TX-N3-M0		None
3	T2-N2-M0	TX-N3-M0	TX-N3-M0		None
4	T4-N3-M0	TX-N3-M0	TX-N3-M0		None
5	T4-N1-M0	TX-N1-M0	TX-N1-M0		None
6	T4-N0-M1	T4-N1-M1	T4-N3-M1	N1=ipsilateral hilar lymph node N3=not identified	None
7		Not Specified	Not Specified		None
8	T2-N1-M1	TX-N1-M0	TX-N1-M0	M0= Direct extension of tumor to ipsilateral hilum	Left Pneumonectomy, No lymph nodes involved, contact with mediastinal and visceral pleura
9	T3-N3-M0	T4-N2-M1	TX-N2-M1	T4=pleural effusion, M1= bone metastasis	None
10	T2-N0-M0	TX-N3-M0/1	TX-N3-M1/0	N3=contralat. Mediastinal LN, M1= second focus located either in lower lobe (=M0) or in upper lobe (=M1)	Surgery 6/11/97, T4-N2/3-M0
11	T2-N0-M0	TX-N0-M1	TX-N0-M1		Left lower lobectomy and wedge resection of Left superior lobe: 3 lesions in LLL, 1 lesion in the LUL.
12	T2-N0-M0	TX-N0-M0	TX-N0-M0		None
13	T2-N2-M0	TX-N0-M0	TX-N2-M0		None

Data Source: Appendix 16.2 Table 13, Vol. 1.38, pg. 0112. *TX= spatial resolution insufficient to allow for specific localization

Sponsor's Efficacy Conclusions:

Technetium Tc 99m P829 may have potential for gamma scintigraphic imaging of primary tumor and metastatic spread of non-small cell cancer of the lungs. Technetium Tc 99m P829 results agreed with histopathology in all 12 patients (100%) for whom histologic proof of disease was obtained. Technetium Tc 99m P829 results agreed with TNM staging at study entry for 6 of 12 patients (50%). For the six patients whose TNM staging and Technetium Tc 99m P829 results were different, Technetium Tc 99m P829 images generally detected more regional lymph nodes and metastases than the TNM staging at study entry.

Technetium Tc 99m P829 results agreed with FDG-PET results for "N" and "M" classifications for 10 of 12 patients (83.3%). Where results of the two procedures were different, Technetium Tc 99m P829 images detected more extensive lymph node involvement than FDG-PET scans.

The majority of images considered optimum were acquired between 3 to 5 hours post-injection.

The results of this study indicate that Technetium Tc 99m P829 may have potential for the safe and effective gamma scintigraphic detection and localization of primary and metastatic tumors of non-small cell cancer of the lungs. The agreement rate between Technetium Tc 99m P829 results and histopathology in this study was 100% in 12/12 patients. No adverse events were noted.

Safety : No adverse event were noted during the study. No other safety parameters were monitored.

Deaths: 0

Withdrawals due to an Adverse Event: 0

Serious Adverse Events: 0

Severe Adverse Events: 0

Extent of Safety:

Radiochemical purity was at least 94% for all injections, with a mean of 97.5%. The average volume injected was 0.8 mL and the mean injected radioactive dose was 18.7 mCi (range 16.0 - 22.0 mCi). Three patients received more than the maximum 19.5 mCi dose specified in the protocol. The mean injected peptide dose was not provided. The protocol specified for 50µg of P829 peptide to be administered. The Lot number used for this study was 9609B02B, which was the to-be-marketed formulation utilizing the heated dose preparation.

Sponsor's Safety Conclusions: No adverse events were reported during the course of the study.

Pivotal Trial Design

Reviewer's Discussion:

Design: The design of this protocol appears to be adequate for the objectives of this Phase 2 study. Points of concern that should be addressed in subsequent studies would be the following:

- Instituting a lesion tracking system to guarantee a one to one correlation of lesion for all diagnostic modalities used.
- Performing all diagnostic modalities within a reasonable time frame to assure comparable clinical state of the patient.
- Analysis plan to assess affect of treatments (chemotherapy, radiation) if performed in recent proximity prior to test drug administration.

The performance of an adverse event profile as the entire safety analysis is not adequate. Given this drug to be investigational, adequate safety assessments, such as vital sign assessments, hematology and serum chemistries and urinalysis assessments should have been performed. If it was the Sponsor's contention that from previous studies these tests were found to be unaffected, then the Sponsor should have provided a rationale for excluding them from the safety assessment.

Efficacy:

The primary efficacy endpoint was the patient-based rate of agreement between Tc99m P829 and histopathology. A more appropriate endpoint would have been a lesion based-rate of agreement.

Results of the direct comparison of the number of lung lesions identified (both primary and metastatic) by FDG-PET and Tc99m P829 images showed good correlation between the two modalities. However, lesion localization and direct comparison by lesion was not clearly assessed.

The data provided shows promising efficacy results that would warrant further investigation, however, this data was collected in a very small patient population. The use of the tumor staging system with scintigraphy is unique and may prove difficult with the degree of anatomical resolution seen with scintigraphic imaging. This too, would need further investigation. The investigator reported an optimum imaging time of 3-5 hours post-dose.

Safety: No adverse events were reported for this study. No specific comments about safety can be made because the Sponsor's planned safety analysis was not inclusive of all parameters that are usually studied during drug development under an IND.

Reviewer's Conclusions:

The study provides supportive data that Tc99m P829 localizes in non-small cell lung tumor when compared to the clinical use of PET-FDG. The clinical significance of these findings can not be determined at this time. No adverse events were reported. Overall safety cannot be established due to a paucity of safety monitoring.

Note: Although PET-FDG is sometimes used as a clinical diagnostic test for cancer, at the present time, it is not approved for that indication.

**Summary Of Non-Pivotal
Phase 3 Studies**

6.5 Summary of Non-Pivotal Phase 3 Clinical Trials

Study P829-30A and B:

These two studies followed identical protocols but each had separate and independent groups of patients, investigators and image readers. These studies were multi-centered, single dose, within-patient comparative, open-label studies enrolling patients with a documented clinical history of neuroendocrine tumor thought to express somatostatin receptors. Each patient had an Indium In-111 Pentetreotide (6 mCi of In-111, 10 µg of peptide) study as part of the enrollment criteria. Patients received approximately 20mCi of heated or unheated Tc99m P829 (50µg of peptide). Focal planar and SPECT imaging followed dose administration. Blinded nuclear medicine physicians did a paired reading of the Tc99m P829 and In-111 Pentetreotide images per region of the body. The primary indicator of efficacy was the patient-based rate of agreement with a final institutional diagnosis (results of diagnostic modalities including In-111 Pentetreotide).

Results of both studies (N=243) showed comparability of Tc99m P829 in all regions of the body except the abdomen. It is anticipated that this discordance is related to the elimination pathway of the drug. Delayed imaging, as performed with In-111 Pentetreotide, might resolve the problems with non-specific binding seen in the abdomen and should be investigated by the Sponsor. A total of 34 patients were enrolled with suspicion of lung neoplasia. An analysis of this subgroup showed that Tc99m P829 was comparable to In-111 Pentetreotide with respect to the institutional diagnosis.

As stated above, both the heated and unheated dose preparations were used in these studies. The Sponsor did not do subgroup analyses to identify any efficacy or safety differences between the dose preparations. Overall when the combined safety data was reviewed, no trends in the safety data were identified. The safety of In-111 Pentetreotide was not assessed as part of these studies.

Study P829-32:

This study was designed to look at the ability of the test drug to detect malignant melanoma. This study was terminated early after the enrollment of 66 patients due to the deficiency of histopathologic data which was suggested as the appropriate standard of truth by the Division. A safety review was done for the 66 patients that completed the study. No trends in the safety data were identified. All patients received the heated to-be-marketed formulation.

Full reviews of the above mentioned studies can be found in the Supportive Clinical Studies section (pages 198-255).

**Pivotal Phase 3
Study P829-34A**

6.5.2 Study P829-34A

Phase 3, P829-34A (volumes 1.61-1.66, Additional information submitted with letter dates 7/22/98, 7/24/98, and 8/26/1998).

Date of Study: December 23, 1996 to December 31, 1997

Formulation: [redacted] Market Formulation

Population: Lung Cancer Patients

Protocol Violations and Deviations:

A protocol violation was defined as one of the following: Not satisfying one or more of the inclusion/exclusion criteria, failure to have a chest X-ray, CT scan or histopathology assessment of the main presenting lesion, or administration of Tc99m P829 with a radiochemical purity of <90%. Protocol violations were identified for 24 of the 128 patients enrolled. Twelve patients violated the inclusion criterion that required a suspicion of cancer in the lung or that the patient be scheduled to obtain a histopathology specimen. Eleven of these patients had undergone histopathology evaluation prior to enrollment in the study as per the Sponsor, however, further review identified a total of 33 patients who had biopsy prior to enrollment (Source: Supplement submitted after NDA filing, Letter date 8/26/98, pg. 0225), see comment below. One patient (Patient 12-03) was enrolled for staging of metastatic disease. Enrollment of the 12 patients identified as protocol violators was approved by the sponsor. Eight patients had no histopathology specimen obtained (or had an inadequate specimen), and are among the patients excluded from the efficacy evaluable population. Other violations which occurred in one patient each are the following: previous enrollment in the study, recent use of an investigational drug, prior surgical resection of the presenting tumor or mediastinal region, recent radionuclide study with Technetium Tc-99m, Indium In-111, or Gallium Ga-67, no CT scan obtained, and no chest X-ray obtained. did not have a histopathology specimen obtained.

A protocol deviation was defined as one of the following: failure to collect baseline vital sign or laboratory data, failure to collect post-injection vital sign or laboratory data, timing of imaging outside the time windows specified by the protocol, activity injected above 22.0 mCi or below 13.5 mCi and improper reconstitution of study drug. Protocol deviations were reported in 65 of 128 (51%) patients enrolled. The most common deviations were the following:

- physical exam performed >14 days prior to injection of Tec99m P829 (23/128)
- injection of <13.5 or >22.0 mCi of Tc99m (26/128)
- whole body imaging performed <45 minutes or >90 minutes post-injection of Tc99m P829 (7/128)
- planar SPECT imaging <90minutes or >5hours post-injection of Tc 99m P829 (7/128)
- missing baseline laboratory data (7/128)

With the exception of patients with missing histopathology or imaging results, patients with protocol violations and deviations were included in all efficacy evaluations.

Comment: The following is a representative sample of problems regarding the quality of the data submitted for review. The significance of the data presented below not only calls into question the validity of the data, but may also have direct impact on the efficacy results. The Sponsor identified 11 patients as having biopsy prior to enrollment, however, in several places within the NDA, a larger number of these violations were identified by this reviewer. For example, comparing enrollment dates with biopsy dates using Appendix 16.2.10.3 (Vol. 65 pg. 0300) and Appendix 16.1.6 (Vol. 63 pg. 003) 34 patients are identified as having biopsy prior to enrollment and thus prior to Tc99m P829 imaging. Using the Supplement submitted after NDA filing, Letter date 8/26/98 pg. 0225, 33 patients were identified as having biopsy prior to enrollment thus prior to Tc99m P829 imaging. Biopsy prior to imaging:

- 1.) Violates the inclusion criteria that states patient must have suspicion of lung cancer.*
- 2.) Can lead to conscious or subconscious enrollment of patients with particular tumor types that have a known propensity to express somatostatin receptors on their surface.*
- 3.) Can potentially lead to altered anatomy depending on the type of biopsy procedure.*
- 4.) Can lead to a positive Tc99m P829 image due to inflammation resulting from the biopsy procedure.*

Other protocol violators were identified but not reported in the study report by the Sponsor. Six patients were found to have had histopathology specimen greater than 6 weeks of enrollment which violates an inclusion criteria (Source: Supplement submitted after filing, Letter date 8/26/98, pg. 225 Vol. 61), however, in the Sponsor's Table 1.4.0 (Vol. 61, pg. 131) only 3 patients were identified as violating this inclusion criteria. The number of patients reported as having violated this criteria is small and not expected to alter the overall results, however, the fact that the number of violations is not constant among sources within the NDA is the issue.

Disposition: A total of 128 patients were enrolled at 11 of the planned 15 study sites within the United States. Of those enrolled, 103 patients completed the study per protocol. Of the 25 patients who did not complete all study procedures, 13 patients did not complete all safety assessments, 5 patients did not complete P829 imaging, 1 patient did not complete all safety assessments or P829 imaging due to technologist error, 1 patient did not complete CT imaging and 8 patients did not have histopathology evaluation performed. (Note: 3 patients were counted twice because they fell into two categories). No patients withdrew consent or dropped out due to an adverse event. One patient was enrolled in the study twice, as patient 1-22 and again as patient 1-23. The second enrollment was used for purposes of safety and efficacy analyses because technically inadequate images were obtained after the first injection. Of the 128 patients who were studied, 112 were analyzed as efficacy evaluable (EEv). Thirteen patients were excluded for lack of histopathology results, 2 patients were excluded for not completing Tc99m P829 imaging and one patient was excluded for not completing the CT imaging and not having histopathology. Please see Tables 1 and 2 for further information regarding patient disposition.

6.5 Pivotal Phase 3 Clinical Trials

6.5.1 Pivotal Trial Design

The phase 3 pivotal trial design for this NDA has evolved over the course of two years. Both pivotal studies (829-34 A & B) utilized the same protocol. The original protocol dated at 12/3/1996 was amended 3/10/1997, 7/14/1997 and 12/8/1997. The following description of the protocol will include those amendments which are crucial to the understanding of the evolution of the protocol as it stands for the purpose of efficacy and safety review for the NDA. Each amendment will be incorporated into the final protocol description so that an immediate comparison of the changes can be appreciated by the reader. The wording used in the original protocol, which was deleted, will be highlighted as italicized text. The final protocol (12/8/1997) will be presented in non-italicized text with those modifications which were different from the original protocol bolded. This review does not address the statistical amendments made (please see Statistical review).

Title: A Multicenter Study Evaluating The Safety And Efficacy Of Technetium Tc99m P829 For The Detection And Localization Of Cancer In The Lung. (The original protocol read as *of Non-Small Cell Lung Cancer.*) Amendment Date (AD) 3/10/97

Objectives:

- 1.) To evaluate the safety of Technetium Tc99m P829 in patients presenting with **suspicion of cancer in the lung**. (The original protocol read as: *a diagnosis or suspected diagnosis of non-small cell lung cancer.*) AD 3/10/97
- 2.) To evaluate the efficacy (accuracy) of Technetium Tc99m P829 for the detection and localization of primary and metastatic sites (hilar and mediastinal lymph nodes) in patients with **suspicion of cancer in the lung**. (The original protocol read as: *a diagnosis or suspected diagnosis of non-small cell lung cancer.*) AD 3/10/97

Population: Approximately 130 patients will be enrolled based on the following inclusion and exclusion criteria.

Inclusion Criteria:

- 1.) Age \geq 18 years
- 2.) **Patients present with suspicion of cancer of the lung.**
(The original protocol read as *Diagnosis or suspected diagnosis of non-small cell lung cancer, and scheduled for bronchoscopy or mediastinoscopy within the next 30-day period.*) AD 3/10/98
- 3.) Patients must have (pre or post-enrollment) a chest x-ray and computed tomography scan of the chest and upper abdomen within **6 weeks** of enrollment. (original protocol: *4 weeks or are scheduled to be obtained within the next 14 days.*) AD 12/8/97

- 4.) Patients are to be scheduled for a procedure in which a specimen for histopathological confirmation will be obtained **within 6 weeks of enrollment.** AD 12/8/97
- 5.) Karnofsky Performance Status score $\geq 60\%$ within 14 days prior to study enrollment.
- 6.) Written and dated informed consent must be obtained **at the time of enrollment.**
(Original protocol stated: *prior to initiating any protocol-specific procedure.*) AD 3/10/97

Inclusion Criteria that were deleted in amendment 3/10/97

- 1.) *Patient is scheduled for Bronchoscopy or Mediastinoscopy within the next 30 days.*
- 2.) *Biopsy must be ordered before patient is enrolled.*

Exclusion Criteria:

- 1.) Females who are pregnant or lactating or of childbearing potential, unless the possibility of pregnancy can be ruled out by either β -HCG testing or by medical history.
- 2.) Patients who have undergone a nuclear medicine study with Technetium Tc99m in the previous 48 hours or with indium In-111 or gallium Ga-67 in the previous 10 days.
- 3.) Patients who have previously been entered in this study. Patients who have received an investigational drug within 30 days of admission to this study.
- 4.) Patients whose medical condition, associated illness or extenuating circumstances make it highly unlikely that follow-up will be completed.
- 5.) Patients with life expectancy at enrollment of less than 60 days.
- 6.) Patients with active pulmonary infections requiring antibiotics within 1 week prior to study entry. (Original protocol had the following: *patients with sarcoidosis or known hypersensitivity pneumonitis and patients who have undergone surgical resection of the primary tumor or surgery in the mediastinal region will be excluded.*) AD 3/10/97
- 7.) Patients who have already undergone surgical resection of the presenting tumor and or mediastinal region.
- 8.) Patients who are unwilling or unable to comply with the protocol.

Dose:

Satisfactory hydration status should be maintained at all times to reduce radiation exposure to non-target organs. If possible, patients will drink at least on 8-ounce glass of water prior to radiopharmaceutical administration and be asked to void frequently.

Intravenous administration of 15-20mCi of Tc99m P829 (50 μ g of P829 peptide) will occur over 15-20 seconds. Technetium Tc-99m P829 dose should be administered within 5 hours of preparation. (Original protocol stated: *6 hours.*) AD 7/14/97

If the radiochemical purity of the Technetium Tc99m P829 is less than 90%, the preparation should not be used.

Nuclear Imaging Procedure:

Tc99m P829: Anterior and posterior whole body imaging will begin approximately one hour post-dose. Focal planar imaging (anterior and posterior) of any primary, secondary or suspected tumor sites will be obtained approximately 2-4 hours post-dose. Focal planar images of the chest, abdomen and pelvis will be acquired for 1,000,000 counts per image. Focal planar images of the head and neck and extremities will be acquired for 500,000 counts per image. Immediately following planar imaging, SPECT imaging of the thorax will be performed. Imaging data will be collected in digital format and also presented on film.

Computed Tomography: All patients will have a computed tomography (contrast or non-contrast) scan of the chest and upper abdomen within **6 weeks** of enrollment **AD 3/10/97**. If contrast is to be used after Tc99m P829 imaging, the 24 hour follow-up clinical laboratory studies must be performed prior to the contrast injection. **If the CT (without contrast) is done after Tc99m P829 imaging, the CT should not begin until 2-4 hour vital sign assessment and clinical laboratory studies are complete. AD 3/10/97**

If contrast material (non-ionic or ionic) is used, the scan should be obtained during a bolus intravenous injection of contrast material. The scan should consist of contiguous 1 cm thick sections through the thorax beginning near the thoracic inlet. Patients should be scanned in suspended respiration with the arms up during the mediastinal imaging.

Efficacy: Tc99m P829 and CT images will be evaluated by site investigators and by blinded readers. Three blinded Nuclear Medicine physicians will review the P829 images and three blinded Radiologists will review the CT images. Each blinded reader will independently evaluate the images randomly.

Tc99m P829 images will be evaluated for the presence or absence of tumor or metastasis in each of the following areas: Right lung, left lung, mediastinum, hilar area as well as other areas identified with unusual uptake. **CT images for the same areas will be evaluated for abnormalities. AD 3/10/97** Tc99m P829 images will be considered positive if there is focal uptake in any region that is not characteristic of normal biodistribution of tracer. The degree of abnormality will be scored as either:

NEGATIVE -no abnormal localization

POSITIVE - abnormal localization suggesting tumor

INDETERMINATE - unable to make a diagnosis

N/A - not applicable (images not obtained for this region)

Computed tomography images will be considered positive if there is visualization of tumor or metastasis in any region. The degree of abnormality in each of the anatomic regions will be scored as either

NEGATIVE - no abnormal visualization

POSITIVE - visualization suggesting tumor

INDETERMINATE - unable to make a diagnosis

N/A - not applicable (images not obtained for this region)

- Baseline out of normal range, post-injection value still out of range in the same direction with a 25% further increase or decrease from baseline.
- Baseline missing, post-injection value out of normal range
- Baseline out of normal range, post-injection value out of range in the opposite direction.
- Baseline and post-injection values both within normal range, but post-injection value at least 50% greater than or less than baseline value.

Changes in WBC differentials will be individually assessed by each investigator.

Patients will be monitored for adverse events throughout the first hour and again at approximately 24 hours following dosing.

Statistical Analysis:

Efficacy: The primary analysis will determine that the accuracy of Tc99m P829 blinded read relative to the histopathologic diagnosis of the suspected lesion for evaluable patients (patients who successfully complete both Tc99m P829 and CT imaging and for whom the histopathology assessment was obtained). Comparison will be made for each anatomical region insofar as possible. **Because of the potential of sampling error with fine needle aspiration, a negative result obtained by fine needle aspiration the absence of a confirmatory tissue biopsy will not be considered definitive if other modalities suggest the presence of malignancy. If such a sample is not obtained, the case will not be considered evaluable in these patients.** Comparison will be made for each anatomical region insofar as possible. AD 7/14/97

The secondary analysis will determine the accuracy of Tc99m P829 relative to histopathologic diagnosis in the subset (at least 50 patients) of patients defined as presenting with a solitary pulmonary nodule. The subset of non-calcified solitary pulmonary nodules between 1 and 3 cm will also be analyzed. AD 12/8/97 Additional secondary analyses will be conducted to assess the ability of Tc99m P829 to detect metastatic disease. This will be assessed by the rate of agreement of Tc99m P829 and histopathology results of the staging procedures to determine the extent of disease and the accuracy for each of the anatomic regions relative to the institutional diagnosis. AD 7/14/97

An intent to treat analyses will be performed for all patients who receive drug. In these analyses, patients whose Tc99m P829 imaging was not done or was indeterminate will be considered to have results that disagree with histopathology results; patient whose CT was not done, or was indeterminate, will be considered to have results that disagree with the histopathology results.

In addition, for each indicator of efficacy and each reader of the CT images, the results of the CT procedure will also be compared with the histopathology results. The majority blinded read of the CT images will then be compared with the histopathology results. *(Original protocol was reworded slightly different but the intent to make the comparison to CT was originally planned.)*

Ninety-five percent confidence intervals will be obtained for sensitivity and specificity for both procedures as appropriate. McNemar's test will then be used to compare the sensitivity and specificity of Tc99m P829 with those of Computed Tomography.

(The original protocol read as follows: *The primary indicators of efficacy are the patient-based rates of agreement with the final histopathological diagnosis for each of the blinded readers. There are two possible outcomes for the histopathological diagnosis: (1) evidence of non-small cell lung cancer in one or more anatomic regions; and (2) no evidence of non-small cell lung cancer in any of the regions biopsied. The results of the Tc99m P829 imaging or CT will be considered in agreement with the histopathological diagnosis if they conform with the following: 1.) results are positive for non-small cell lung cancer in at least one anatomic region in common with the histopathological diagnosis and 2.) results are negative for non-small cell lung cancer in all the regions biopsied. Secondary indicators of efficacy include patient-based rates of agreement with histopathological diagnosis based on the institution's reading of the Tc99m P829 and CT images and rates of agreement for each of the four anatomic regions. In addition, the associated sensitivity and specificity for each of the agreement rates defined above will be evaluated for Tc99m P829 and CT. For each indicator of efficacy and each blinded reader of the Tc99m P829 images, results of the Tc99m P829 procedure will be compared with the majority blinded read of CT. McNemar's test will be used to test the null hypothesis of no difference between the proportions for Tc99m P829 and CT, versus the two-sided alternative that the proportions are different. AD 7/14/97*

An interim analysis was originally planned to decide whether the use of Tc99m P829 for the detection of primary and metastatic tumors sites associated with non-small cell lung cancer is a feasible indication worth pursuing. This analyses was planned for the first sixty evaluable patients. Deleted in AD 3/10/97

Safety: For vital sign measurements and clinical laboratory tests, the Wilcoxon signed-rank test will be used to analyze changes in each variable at each of the post-drug times. Laboratory test results will also be categorized as below normal range, within normal range or above normal range for pre-drug and post-drug values. The incidence of adverse events and the incidence of clinically significant changes in vital sign measurement and laboratory results post-drug will be statistically summarized and 95% confidence intervals will be obtained for proportions of patients as appropriate.

Subgroup Analysis: Safety and primary efficacy indicators will be summarized and tabulated for demographic subgroups by age, gender, race, renal function, and liver function.