Table 27. Clinical Chemistry Tests: Mean Changes from Pre-Injection Values

Laboratory Test	Statistic[1]	Pre-Injection Value	Change from Pre-Injection Value 2-4 Hours	Change from Pre-Injection Value 18-30 Hours
Alkaline Phosphatase (U/L)	N	120	115	106
	Mean	82.1	-1.5	0.2
	p-value		0.007**	0.603
AST (U/L)	N	125	124	111
	Mean	24.4	-1.1	-1.0
	p-value		0.716	0.273
ALT (U/L)	N	125	124	111
	Mean	22.7	-0.4	-0.8
	p-value		0.053	0.154
Total Protein (g/dL)	N	125	124	111
	Mean	7.06	-0.10	-0.05
	p-value		0.002**	0.431
Total Bilirubin (mg/dL)	N	125	124	111
	Mean	0.49	0.01	0.03
	p-value		0.022*	0.002**
BUN (mg/dL)	N	125	124	111
	Mean	16.0	-0.5	-0.3
	p-value		<0.001**	0.262
Creatinine (mg/dL)	N	125	124	111
	Mean	0.90	-0.02	0.01
	p-value		<0.001	0.389
LDH (U/L)	N	119	113	100
	Mean	190.2	-1.9	-5.8
	p-value		0.648	0.009*

Data source: Section 14.3.5, Table 14.1.0

1 P-values assess the difference between pre-and post-injection values and were determined using the Wilcoxon Signed Rank test

* indicates significance at the 0.050 level; ** indicates significance at the 0.010 level.

Sponsor Text Table 12-D

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Shifts in clinical chemistry parameters were infrequent. Results of the shift table analysis can be found in table 28.

Table 28. Chemistry Shift Table results relative to normal ranges

Parameter	2-4 hrs		18-30 hrs.	
	Increase	Decrease	Increase	Decrease
Alk Phos.	2	3	4	2
AST	3	8	6	6
ALT	0	3	0	4
LDH	4	6	5	6
4	4	5	1	7
Totoal Bili	1	0	2	1
BUN	0	2	0	1
Creatinine	2	3	2	3

Data Source: Table 14.2.1, Population N's for each parameter varied between assessment time: 2-4hr N= 113-124, 18-30hrs N=100-111.

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Most of the shifts in chemistry parameters that produced an increased value occurred when normal values shifted to a high value. Most of the decreases seen in both assessments were values that shifted from high value pre-injection to a normal post-injection value.

The following table presents those changes that represented shifts in laboratory values that met the criteria of a 25% change toward abnormal and that shifted or remained outside of the normal range.

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Table 29. Incidence of Treatment-Emergent Clinically Significant Clinical Chemistry Values

Laboratory Test	Statistic	Post-Injection Evaluation Time	
		2-4 Hours	18-30 Hours
Alkaline phosphatase	CS/N (%) [Patient ID]	1/115 (<1%) [12-09]	1/106 (<1%) [12-09]
AST	CS/N (%) [Patient ID]	4/124 (3%) [1-21, 11-03, 11-17, 12-09]	8/111 (7%) [1-15, 1-29, 5-03, 11-01, 11-02, 11-17, 12-09, 12-13]
ALT	CS/N (%) [Patient ID]	1/124 (<1%) [12-09]	2/111 (2%) [1-29, 12-09]
Total protein	CS/N (%) [Patient ID]	0/124	0/111
Total bilirubin	CS/N (%) [Patient ID]	1/124 (<1%) [12-09]	1/111 (<1%) [12-09]
BUN	CS/N (%) [Patient ID]	0/124	0/111
Creatinine	CS/N (%) [Patient ID]	0/124	0/111
LDH	CS/N (%) [Patient ID]	5/113 (4%) [1-08, 12-03, 12-06, 12-09, 13-06]	7/100 (7%) [1-05, 1-15, 1-18, 5-03, 11-02, 11-03, 12-09]

Data Source: Section 14.3.4, Table 13.1.0
Note: CS=number of patients with a clinically significant change from pre-injection value; N=total number of patients with a pre-injection value and a post-injection value at the specified time point.
Note: NA=Not applicable
Note: Patient ID = patient identification number

Sponsor Text Table 12-F

Tests of liver function

A total of 10 patients had post-injection AST values that met the criteria for a clinically significant change at one or both assessments. Review of individual patient data in Table 13.1.0 shows that 9 of these patients had increases in AST which were <2X the upper limit of normal (ULN). Patient 12-09, a patient with a complex medical history, including hepatic cirrhosis, hepatitis, and human immunodeficiency virus (HIV), had high post-injection AST values (294 U/L and 277 U/L), with no pre-injection value available for comparison. Only one patient's AST changes were considered, by the investigator, to be possibly related to Technetium Tc 99m P829; Patient 5-03 had an increase from a pre-injection value of 18 U/L to post-injection of 44 U/L. No follow-up values were available for any patient.

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Two patients had post-injection ALT values that met the criteria for clinical significance at one or both assessments. Patients 1-29 had values above the normal range at all assessments including pre-injection and patient 12-09 (the patient with a history of cirrhosis, hepatitis, and HIV disease) had high post-injection ALT values of 164 U/L and 159 U/L, with no pre-injection values available.

One patient had post-injection bilirubin values which met the criteria for clinical significance. Patient 12-09 (the patient with a history of cirrhosis, hepatitis, and HIV disease) had high bilirubin values of 2.6 mg/dL and 2.2 mg/dL at 2 to 4 hours and 18 to 30 hours, respectively. No other patient had any bilirubin value exceeding the upper limit of the normal range.

Other enzymes

Patient 12-09 (the patient with a history of cirrhosis, hepatitis, and HIV disease) had high post-injection alkaline phosphatase values of 207 U/L and 209 U/L, with no pre-injection value available for comparison.

Eleven patients had post-injection LDH values that met the criteria for clinical significance. Six patients (Patients 1-05, 1-15, 1-18, 5-03, 11-02, and 12-03) had normal pre-injection LDH values and one or more post-injection values exceeding the upper limit of the normal range; all values were <2X the ULN. No follow-up measurements were available for any of these patients. Two patients (Patients 1-08 and 13-06) had transient elevations in LDH at 2 to 4 hours post-injection, with values returning to the normal range at 18 to 30 hours and three patients (Patients 11-03, 12-06, and 12-09) had high post-injection LDH values with no pre-injection values available for comparison.

Summary of Clinically Significant Laboratory Values (as per the Sponsor)

A total of 20 patients had one or more post-injection clinical laboratory results that met the criteria for a clinically significant change. Three additional patients had no baseline data but had post-injection values outside of the normal range. With few exceptions, most patients had a single clinically significant value for a single laboratory parameter, and nearly all of the values flagged as clinically significant were considered unevaluable or not clinically significant by the investigators. The most common changes were reported for AST and LDH; all of the increases in these laboratory parameters were <2X the upper limit of normal.

It should be noted that no treatment-emergent changes in clinical laboratory tests were reported as adverse events.

Comment: As per the protocol, all laboratory parameters with significant changes were to be repeated at specific intervals following the procedure until the values returned to pre-injection values or until the investigator and the monitor agreed that further follow-up was no longer clinically required. No lab values were followed by the investigator beyond the 18-30hr. assessment regardless of the abnormality of the value.

Vital Sign Assessments:

Pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiration rate, and oral temperature were recorded immediately prior to injection (baseline) of Technetium Tc 99m P829, and at approximately 5, 30 and 60 minutes, and 2 to 4 hours, and 18 to 30 hours post-injection.

Summary statistics for changes in vital signs from pre-injection values at each post-injection assessment are summarized in table 30. Review of summary statistics for vital sign data revealed no clinically important trends in measured values over time. Review of summary statistics for changes in vital signs also revealed no clinically important trends, although some changes from pre-injection measurements for pulse, systolic blood pressure, and diastolic blood pressure were statistically significant from baseline. Mean changes in pulse ranged from -1.5 to -2.1 bpm through 2 to 4 hours post-injection (all p values <0.001); at 18-30 hours, the mean change in pulse was -0.2 bpm (p-value=0.799). Mean changes in systolic blood pressure were -2.1, -2.1, -2.4, and -3.2 mmHg at 5, 30 and 60 minutes, and 18-30 hours, respectively (all p-values ≤0.001); at 2-4 hours, the mean change in systolic blood pressure was -1.4 mmHg (p-value=0.087). Mean changes in diastolic blood pressure were <1 mmHg at all assessments except 18-30 hours (mean change, -1.6 mmHg; p-value=0.020).

Table 30. Vital Signs: Mean Changes from Pre-Injection Values

Parameter	Pre-Injection	Post-Injection Evaluation Time:				
		5 min	30 min	60 min	2-4 hr	18-30 hr
Pulse (bpm)	76.5 ± 1.0	-1.5 ± 0.4*	-1.9 ± 0.5*	-1.6 ± 0.5*	-2.1 ± 0.5*	-0.2 ± 0.7
SBP (mmHg)	130.8 ± 1.7	-2.1 ± 0.6*	-2.1 ± 0.7*	-2.4 ± 0.7*	-1.4 ± 0.8	-3.2 ±1.08*
DBP (mmHg)	76.0 ± 1.0	-0.6 ± 0.5	-0.7 ± 0.5	-0.4 ± 0.5	-0.1 ± 0.5	-1.6 ± 0.7**
Respiration (b/min)	18.6 ± 0.3	-0.1 ± 0.1	-0.2 ± 0.2	-0.3 ± 0.2	-0.2 ± 0.2	-0.3 ± 0.2
Temperature (°F)	97.9 ± 0.1	0.0 ± 0.0	0.0 ± 0.1	-0.1 ± 0.1	-0.1 ± 0.1	0.1 ± 0.1
Data Source: Section 14.3.6, Table 15.1.0						

*** Statistically significant p≤0.001 ** Statistically significant p=0.02 Sponsor Text Table 12-G**

Four patients had clinically significant changes in pulse and one patient had a clinically significant change in SBP. The following is the Sponsor's summary of these changes.

Patient 5-10 had a pulse of 68 bpm prior to injection of Technetium Tc 99m P829; at 18 to 30 hours post-injection, the patient's pulse was 88 bpm, an increase of 20 bpm. No clinical symptoms were associated with this increase in pulse.

Patient 6-01 had a 20-bpm decrease in pulse at the 2 to 4 hours post-injection (96 bpm) relative to the pre-injection measurement (116 bpm). Systolic pressure was relatively constant however, diastolic pressure dropped by 20mmHG from a baseline value of 72 mmHg to a 2-4 hour value of 52mmHg. Respiration and temperature also remained constant.

Patient 12-02 had a 26-bpm decrease in pulse at the 2-4 hours post-injection (78 bpm, measured during scanning) relative to the pre-injection measurement (104 bpm); at 18 to 30 hours, the patient's pulse was 82 bpm.
Patient 12-12 had a 22-bpm decrease in pulse at 2 to 4 hours (88 bpm) relative to the pre-injection measurement (110 bpm); at 18 to 30 hours post-injection, the patient's pulse was 84 bpm.
Patient 8-05 had a pre-injection SBP of 155 mmHg,
which remained relatively stable at subsequent assessments through 2 to 4-hours post-injection; at 18 to 30 hours, the patient's SBP was 120 mmHg.
None of these changes were judged by the investigators as related to the use of Technetium Tc 99m P829.

Sponsor's Safety Conclusions
In study, a single intravenous injection of Technetium Tc 99m P829 was well-tolerated by patients undergoing evaluation of possible cancer in the lung. No serious adverse events were reported and none of the patients discontinued the study due to adverse events.
Only 8 of the 128 patients experienced adverse events, all events were judged to be of mild or moderate severity. The most frequently reported adverse event was headache reported in 3 patients.
Changes in laboratory values over time were small in magnitude and were not clinically significant. Furthermore, for most laboratory parameters, the numbers of patients with shifts from baseline representing increases and shifts representing decreases were similar, suggesting that no consistent, treatment-related effect is present.
No clinically significant trends in post-injection vital signs were observed; mean changes to each post-injection assessment were small and not clinically relevant.

Comments: *Review of the vital sign data did not show any clinically significant trends given cut off points chosen by the Sponsor. These cut off points, in particular for blood pressure do not appear rigorous enough. There were a few patients that had changes in systolic pressure (most of which were decreases from baseline) occurring 60 minutes or later with no other marked changes in other vital sign parameters measured to suggest any trends. There were few marked changes in pressure within the first 30 minutes post dosing. One patient (12-8) had a drop in systolic blood pressure from 116mmHg to 93mmHg and a drop in diastolic pressure from 88mmHg to 70mmHg at the 5 minute assessment time. Respiration and temperature values at that timepoint were unremarkable. There were no symptoms documented, by the Sponsor, in relation to this drop in pressure.*

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Reviewer's Discussion

Safety: There were 11 adverse events reported in 8 patients. All but 2 adverse events were mild in severity. Two cases of headache were reported as moderate in severity and both required treatment. Three adverse events were judged by the investigator as possibly related to test drug administration: 2 cases of headache and one case of nausea. Only one adverse event (chest pain) had its onset within the first hour post-drug administration. The remaining adverse events were reported within the first 24 hours post-injection, however, they do not appear to be directly related to the study drug. Patients reporting leg an back pain had the onset of their symptoms around the time of imaging suggesting a relationship between the imaging procedure (not test drug) and the adverse event.

The white blood cell count differential appeared to vary the most with regards to baseline hematology values. Clinically significant variations were seen in basophil, eosinophil, monocyte and lymphocyte counts. In most patients with clinically significant changes in basophil and eosinophil counts, values remained within the normal range. No consistent trend in eosinophil counts was seen to suggest any allergic response. Even though statistically significant mean decreases from baseline were seen for hematocrit and hemoglobin at the 2-4 hour timepoint, no clinically relevant trends were identified.

Serum chemistry parameters did not show any clinically relevant trends. Most statistically significant changes in liver function and renal function tests were found to be decreases.

The Sponsor did not include normal ranges for vital sign data, subsequently, values pre and post-injection were not flagged as being abnormally high or low and shift table and scatter plot analyses were not performed. The main review centered around those patients having clinically significant changes as identified by the Sponsor. Review of this data did not identify any specific trends in any of the vital sign parameters.

Overall, the cut off points chosen by the Sponsor for clinically significant changes in blood pressure and for identification of outliers for the scatter plot analysis did not allow for a rigorous assessment to identify trends within the data.

Efficacy: Execution of this study resulted in a multitude of protocol violations and deviations. Not all violations and deviations have direct impact on efficacy results but their presence suggests poor adherence to the inclusion/exclusion criteria. To further stress this point, several patients that had violations were not reported in the text portion of the study report by the Sponsor. A majority of patients had biopsy prior to enrollment which was identified as violating the inclusion criteria: suspicion of lung cancer. This violation has the potential to impact on the efficacy analysis since biopsy prior to enrollment and thus prior to P829 imaging could:

1.) Lead to the conscious or subconscious enrollment of patients with particular tumor types that have a known propensity to express somatostatin receptors. However, review of the patients with biopsy prior to enrollment did not show any significant bias by the Sponsor to enroll patients with a particular tumor type (namely small cell lung cancer) that has a known propensity to express somatostatin receptors.

2.) Lead to altered anatomy (depending on biopsy type). Most of the biopsy procedures used for these patients were needle biopsy, one of the less invasive procedures.
3.) Lead to a positive Tc99m P829 image due to inflammation resulting from the procedure itself. This issue would result in a larger number of falsely positive cases and thus a lower specificity. This finding was not seen. The Sponsor should have analyzed the efficacy data by biopsy prior to and post-Tc99m P829 imaging to assess if having a biopsy prior to imaging had any impact on the efficacy results.

Protocol deviations were reported in 51% of the patients, unfortunately, the actual deviations were not specified in the study report. Instead, the Sponsor presented the deviations as either X or Y. For example, deviations in dose were reported as an injection of <13.5 mCi or >22.0mCI of Tc99m. The actual deviation per individual patient was not specifically reported. Alterations in dose and imaging time need to be accurately reported. The breakdown of patients per dose and image time deviation should have been reported and if the numbers were found to be high per subgroup, an analysis to identify any impact on efficacy that may have resulted should have been studied.

Protocol violations were found to be underreported in this study. When reviewing the Sponsor's inclusion and exclusion criteria and applying it, it was found that the Sponsor underreported the number of patients who had biopsy prior to enrollment. It was also found that biopsy dates were inconsistent from source to source within the NDA. These findings led to concerns about the quality of the data. The impact of this issue on the outcome of this review is unknown. A site inspection by the Division of Scientific Investigations, did not report any unusual findings.

The in vitro receptor assay data was very limited for this study. This data with other pre-clinical in vitro receptor binding assay data, however, supports the mechanism of action of this drug. The specific binding to somatostatin receptors expressed on the surface of tumor is the vital basis for the Sponsor's pivotal phase three investigation. The correlation of Tc99m P829 with the diagnosis of malignancy by histopathology was used to assess the ability of this agent to detect benign from malignant disease. It is important to acknowledge that Tc99m P829 will bind somatostatin receptors expressed on normal and abnormal (benign and malignant) tissue. Therefore, the results of this study need to be correlated with other diagnostic tests, as well as patient symptoms, and medical history.

The Sponsor's primary efficacy endpoint was the accuracy of Tc99m P829 compared to histopathology for the diagnosis of malignant tumor in the lung. As stated in the review of the protocol, the division requested that the Sponsor provide sensitivity and specificity analysis in support of the primary efficacy endpoint.

This study was driven by two primary sites of enrollment, site 1 providing 25% of the population and site 11 enrolling 23% of the population. The remainder of the population was distributed over 9 other sites. Both site 1 and 11 were located in the United States.

Of the 112 patients with efficacy evaluable results, 30% had biopsy prior to enrollment and thus, prior to Tc99m P829 imaging. Any intervention prior to imaging with the test drug has the potential to influence the outcome.

This is a design flaw that at the very least needs to be addressed and analyzed by the Sponsor to determine if biopsy prior to imaging had any influence on the efficacy results.

The adjacent region algorithm analysis, which the Sponsor used to support efficacy, was a post hoc addition to the analysis plan. The introduction of this analysis plan occurred after an initial ITT analysis was performed on the data. As per the Sponsor, the reason for such a change was inconsistency in primary lesion location when compared to biopsy location. This discrepancy resulted in a one-to-one algorithm negative result which became positive on the adjacent region algorithm in 18 patients pooled for all three blinded readers. Comparison of the primary efficacy analysis per blinded reader and algorithm can be found in table 31.

Table 31. Primary Efficacy Results per Reader and Algorithm*

ALGORITHM AND READER	SENSITIVITY (%)	SPECIFICITY (%)	AGREEMENT (%)
Adjacent			
Reader 1	83	64	79
Reader 2	82	61	77
Reader 3	79	64	75
Majority	82	61	77
One-to-One			
Reader 1	74	79	75
Reader 2	67	79	70
Reader 3	71	93	77
Majority	70	86	74

*** These data are the Sponsor's reported results. Please see FDA's statisticians review for confirmation of this data.**

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The sensitivity seen in the one-to-one algorithm read is poor and hovers around 70%. The sensitivity increases with the adjacent region algorithm to the low 80% range. Specificity improves with the One-to-one algorithm analysis. The Sponsor's reasoning for the adjacent region algorithm analysis is not adequately supported. The diagram of adjacent lung regions that supports the adjacent region algorithm, proposes a very liberal agreement potential as compared to the strict one-to-one algorithm. In order to accept this post hoc analysis, it would be necessary for the Sponsor to provide an analysis of those cases which show a negative result for the one-to-one region that becomes positive for the adjacent region per blinded read. This analysis should incorporate the actual CT findings (CRF) and images, the actual pathology report and the Tc99m P829 images results (CRF) and images with adequate discussion to show that these regions were in close enough proximity for the blinded readers to have made a realistic mistake in their localization identification. It appears that the real problem began with discordance between CT localization and histopathology localization. Therefore, since CT was used to direct biopsy, the type of biopsy should also be specified with the above information. It is not clear where the Sponsor thinks the problem in localization occurred and how their analysis plan corrected for the problem. The statement that differences were seen in location identification just proves that accuracy in lesion tracking was a problem. The significance of this problem is not fully known.
It is interesting to note that the primary investigator, who had all the information at the time of his read, identified 13 cases as false negative by one-to-one algorithm but positive when the adjacent algorithm was employed. It is suggested that the one-to-one algorithm be used in support of this NDA.

Solitary pulmonary nodules was a subgroup analyzed as a secondary endpoint. The definition of SPN that was applied for this analysis is not known. In the strictest sense, the definition of SPN is a solitary lesion without other abnormalities including adenopathy. Review of both the site CT results and the CT results presented in the demographics section reveals patients which were categorized as having a SPN but had other regions reported as abnormal on CT.

The results from the SPN analysis shows that there is poor sensitivity and specificity with lesions between 1-3 cm in size. As size increases, sensitivity and specificity results increased. There appeared to be significant variability seen between readers for this analysis, however, the Sponsor did not do a kappa statistic to test for this. Given the earlier comments regarding the definition of SPN applied and the marked interreader variability demonstrated here, these findings should not be referred to in labeling. The reasoning for the lack of analysis of the subgroup of patients with solitary pulmonary nodules between the 3 and 6 cm size is not known. Confirmation of the total number of patients presenting with SPN will need to be provided.

The comparison of CT to histopathology for purposes of diagnosis of malignancy versus benign disease was carried out as a secondary endpoint. This analysis showed relatively good sensitivity but poor specificity of CT for distinguishing benign from malignant disease.

The post hoc staging analysis and analysis reported by disease subgroups did not yield any significant information.

Pivotal Phase 3
Study P829-34B

6.5.3 Study P829-34B

Pivotal Phase 3, P829-34B (Volumes 1.67-1.73, Additional information submitted with letter dates of 7/22/98, 7/24/98 and 8/26/98).
Date of Study: December 23, 1996 to December 31, 1997
Formulation: [redacted] Market Formulation
Population: Lung Cancer Patients

Study P8929-34B followed the same protocol format and design as study P829-34A.

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 15 of the 142 patients enrolled. Twelve of the 15 did not have a histopathology specimen obtained. These 12 were excluded from the efficacy evaluation. Of the remaining three patients, one did not have a chest X-ray and 2 patients had active pulmonary infections requiring antibiotics within one week prior to enrollment (5-38, 8-03).

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 42 of 142 patients enrolled. The most common deviations were the following:

-physical exam performed >14 days prior to injection of Tc99m P829 (15/142)
-injection of <13.5 or >22.0 mCi of Tc99m (14/142)
-whole body imaging performed <45 minutes or >90 minutes post-injection of Tc99m P829(11/142)
-missing baseline laboratory data (9/142)

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 Sponsor does not identify any patients as having violated the inclusion criteria of having suspicion of lung cancer leading to biopsy prior to enrollment as were identified in study P829-34A. Review of the data reveals that 63 (44%) patients had biopsy prior to enrollment and thus prior to Tc99m P829 imaging (Source: Supplement submitted after NDA filing, Letter date 8/26/98 pg. 0228). Biopsy prior to imaging:
1.) Violates the inclusion criteria as patients having a suspicion of 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.

One other protocol violations in which the Sponsor under-reported the number of violators is as follows: Seven 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. 228), however, in the Sponsor's Table 1.4.0 (Vol. 67 pg. 133) only 4 patients are identified as having violated this inclusion criteria.

Disposition: A total of 142 patients with suspicion of lung cancer were enrolled at 13 investigative sites (10 United States and 3 European). Of those enrolled, 109 (77%) patients completed the study per protocol. Of the 33 patients who did not complete all study procedures, 13 patients did not complete all safety assessments, 6 patients did not complete P829 imaging and 14 patients did not have histopathology evaluation performed. No patients withdrew consent or dropped out due to an adverse event. Of those patients that did not complete the safety assessments, the most common reasons include refusal/unable to return for the 24 hour assessment and technical difficulties with the shipment of laboratory specimens. Of the 14 patients that did not have histopathology evaluation, 8 had no specimen obtained and 6 had an inadequate, non-diagnostic or non-lung specimen obtained. No patients discontinued from the study due to an adverse event. Patient disposition is displayed in Tables 1 and 2.

Table 1. Patient Disposition at Study Completion For All Enrolled Patients

	Statistic	All Patients
Total number of patients	n	142
Number of patients who completed the study per protocol	n (%)	109 (77%)
Number of patients who did not complete all study procedures:[2]	n (%)	33 (23%)
Completed Technetium Tc 99m P829 imaging, but did not complete safety assessments	n (%)	13 (9%)
Completed safety assessments, but did not complete Technetium Tc 99m P829 imaging	n (%)	6 (4%)
Did not complete Technetium Tc 99m P829 imaging or safety assessments	n (%)	0
Did not complete computed tomography imaging	n (%)	0
Did not have histopathology evaluation of lesion	n (%)	14 (10%)
Reason patients did not complete all study procedures		
Withdrew consent	n (%)	0
Adverse event	n (%)	0
Lost to follow-up	n (%)	2 (1%)
Other	n (%)	32 (23%)

Data Source: Section 14.1, Table 1.1.0
1 Percentages are based on the total number of patients.
2 Three patients reported two completion status, See Figure 10-A.

Data Source: Vol. 67 page 45 Sponsor Table 10-A.

Table 2. Disposition of Patients by Study Site

PARAMETER	ITT POPULATION	EFF POPULATION
Total Number of Patients	142	114
Total Number of Patients per Study Site		
Site 1	34 (24%)	30 (26%)
Site 2	2 (1%)	0
Site 3	2 (1%)	1 (1%)
Site 4	5 (4%)	2 (2%)
Site 5	38 (27%)	29 (25%)
Site 6	1 (1%)	0
Site 7	15 (11%)	15 (13%)
Site 8	24 (17%)	18 (16%)
Site 9	2 (1%)	2 (2%)
Site 12	7 (5%)	5 (4%)
Site 13	2 (1%)	2 (2%)
Site 15	5 (4%)	5 (4%)
Site 16	5 (4%)	5 (4%)

Data Source: Vol. 67 Section 14.1 Table 1.0.0, ITT= intent-to-treat and EFF= efficacy evaluable.

Exposure: All patients received a single intravenous injection of Technetium Tc 99m P829 at a dose of 50 μg P829 peptide radiolabeled with 15 to 20 mCi of Technetium Tc 99m over 15 to 20 seconds. Investigators prepared the radiolabeled peptide using a kit containing 50 μg of P829 peptide and sufficient Technetium Tc 99m to administer 15 to 20 mCi of activity, using the entire contents of the vial. Contents of the kit were heated during the course of dose preparation. In the efficacy evaluable population, the mean injected dose of P829 peptide was 42.6 μg and a mean injected radioactivity dose was 19.0mCi. There were 13 (11%) efficacy evaluable patients who received a mCi dose of greater than 22mCi. The highest mCi dose administered to any patient was 32.8 mCi. Volumes of injected dose ranged from 0.40 - 2.3ml. The Lot numbers used for the study are 9509B01D, 9609B02C, 9609B02E, and 9609B02F, 9609B02G and 9609B02H.

Demographics: The Sponsor's table below (Table 3) compares demographic data between the Intent-to-Treat (ITT) population and Efficacy Evaluable population. Height and weight demographic information for the efficacy evaluable population can be found in Table 4. Among the 142 patients in the ITT population, the most common abnormalities or diseases reported were respiratory disease (72%); cardiovascular disease (62%); gastrointestinal disease (40%); musculoskeletal disease (39%); diseases of the eye, ear, nose, and throat (37%) and genitourinary disease (34%). Physical examinations were performed prior to injection of Technetium Tc 99m P829 and abnormalities were recorded by body system. Abnormalities of the lung were present in 53 of 142 patients (37%). Other body systems with abnormalities reported for 10% or more of patients were: head, eyes, ears, nose, and throat (16%); skin (12%); extremities (12%); and musculoskeletal (10%).

Table 3. Demographic and Background Characteristics For Safety and Evaluable Populations

Parameter	Statistic	Safety/ITT Population	Evaluable Population
Total number of patients	n	142	114
Age (years)	n	142	114
	Mean	65.1	65.6
	Median	67.0	67.0
	SE	0.94	0.99
	Min, Max	29, 86	37, 86
Gender			
Male	n (%)	96 (68%)	77 (68%)
Female	n (%)	46 (32%)	37 (32%)
Race			
Caucasian	n (%)	103 (73%)	80 (70%)
Black	n (%)	11 (8%)	8 (7%)
Hispanic	n (%)	2 (1%)	2 (2%)
Native American	n (%)	0	0
Asian/Oriental	n (%)	26 (18%)	24 (21%)
Other	n (%)	0	0
Karnofsky Performance Status (%)	n	142	114
	Mean	92.6	92.6
	Median	100.0	100.0
	SE	0.80	0.91
	Min, Max	60, 100	60, 100
Chest X-ray			
Normal	n (%)	3 (2%)	3 (3%)
Abnormal	n (%)	138 (97%)	110 (97%)
CT Scan			
Normal	n (%)	2 (1%)	2 (2%)
Abnormal	n (%)	140 (99%)	112 (98%)
Solitary Pulmonary Nodules[1]	n (%)	76 (54%)	62 (54%)
>0 to ≤3 cm diameter	n	44	34
Non-calcified SPN >0 to ≤3 cm diameter	n	42	33
>3 to ≤6 cm diameter	n	28	25
Non-calcified SPN >3 to ≤6 cm diameter	n	25	22
Calcification Evident on Chest X-ray	n (%)	6 (4%)	4 (3%)

Data Source: Section 14.1, Tables 2.0.0, 2.0.1
Note: Percentages are based on the total number of patients.
[1] Based on chest X-ray or CT measurement.

Data Source: Sponsor Text Table 11-A, Vol. 65, pg. 063.

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Table 4. Height and Weight Demographics

Parameter	Efficacy Evaluable Patients
Total Number of Patients	114
Weight (kg)	
Mean	73.0
Median	70.8
Std. Error	1.5
Range	41-106
Height (cm)	
Mean	170
Median	170
Std. Error	0.9
Range	130-189

Data Source: Vol. 67, Section 14.1, Table 2.0.1

Lesion location was determined by the investigator using the histopathology results. There were 15 patients who had more than one lesion diagnosed. The most common locations for the main presenting lesion were the right upper lung lobe (30%) and the left upper lung lobe (20%). Please see Table 5 for full representation of main presenting lesion locations. Nineteen additional lesions were biopsied and reviewed as a secondary endpoint.

Table 5. Main Presenting Lesion

Region of Presenting Lesion	Patients n (%)
RUL	**43 (30)**
RML	**7 (5)**
RLL	**22 (15)**
RH	**5 (4)**
RM	**1 (1)**
LUL	**29 (20)**
LLL	**13 (9)**
LH	**4 (3)**
LM	**1 (1)**
Other	**5 (4)**

N=142, Data Source Vol. 67, Section 14.1, Table 3.0.0

A total of 35 patients received some form of treatment for their lung cancer either prior to enrollment or after enrollment. Seventeen of the 35 patients had treatment within the last 12 months. The type of treatment and timing of that treatment can be found in Table 6. The Sponsor does not give actual treatment dates, therefore the proximity to Tc99m P892 cannot be assessed.

Comment: *Affects of treatment may or may not have influenced uptake of Tc99m P829 and thus altered image results. A separate analysis, to address whether treatment alters the performance of this drug, should be performed.*

Table 6. Cancer Treatment History For All Patients Within the past 12 Months.

Patient Number	Treatment	Time since last treatment
1-8*	Surgery Radiation	7-11month 4-6 month
1-10	Radiation	Unknown
1-12	Radiation Chemotherapy LAG Laser	<1 months 1-3 months <1 month
1-16	Radiation	<1 months
1-17	Radiation	< 1 month
4-4*	Radiation Chemotherapy	<1 month < 1 month
5-7	Radiation	Unknown
5-10	Surgery Radiation Chemotherapy	7-11 months 7-11 months 7-11 months
5-22	Surgery	1-3 months
5-28	Radiation	<1 month
5-30	Surgery	1-3 months
9-2	Surgery	<1 month
12-3	Radiation	4-6 months
12-7	Surgery	Unknown
15-1	Hormonal	<1 month
16-2	Chemotherapy	<1 month
16-5	Chemotherapy	<1 month

***patients excluded from efficacy analysis due to lack of evaluable histopathology assessment. Data Source: Vol. 67, Appendix 16.2.10.5**

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As part of the demographics, the Sponsor did not report the breakdown of patients presenting by tumor type. This information was generated from histopathology information provided in Appendix 16.2.3. The breakdown by tumor type of those patients that had a biopsy can be found in Table 7.

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Table 7. Histopathology Results for All Patients Having a Biopsy

Malignant Histopathology	N	Benign Histopathology	N
Adenocarcinoma	26	Granulomatous disease	5
Squamous Cell	33	Hamartoma	1
Non-Small Cell*	27	Inflammatory Process	5
Carcinoid	2	Bronchial Epithelial cells	1
Large Cell	5	Negative for malignant cells	4
Small Cell	8		
Other**	6		
TOTALS	106		16

***Type of NSC not specified, **Hodgkins Lymphoma, Adenosquamous Ca, Melanoma, Type unspecified. No diagnosis was reported in 8 patients that had a biopsy. Data Source: Appendix 16.2.10.3, Vol. 73.**

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Efficacy Evaluation:

The efficacy evaluable population was comprised of 114 (80%) of the 142 patients enrolled. Of the 28 (20%) patients that were excluded, 26 patients were excluded due to a lack of an evaluable histopathology assessment, one patient did not complete Tc99m P829 imaging and one patient had the primary lesion removed prior to Tc99m P829 imaging.

Comment: The Sponsor identified 26 patients in Table 1.3.0 (Vol. 67, pg. 0129) as having been excluded due to lack of an evaluable histopathologic assessment. When the histopathologic information was reviewed, Appendix 16.2.10.3 (part 3 of 6,Vol. 73, page 055), 6 patients that were excluded by the Sponsor had histopathologic results listed in this appendix. Since histopathology was reported for these patients, these patients should be included in the Sponsor's statistical review as worst case.

Efficacy Results: The Sponsor presented all efficacy results based on the adjacent region algorithm and majority blinded read despite the Division's request to present the primary efficacy results by individual blinded readers on a site to site basis. However, the Sponsor did analyze the results per blinded reader and by a one-to-one algorithm, therefore, the following will provide both presentations for the reader's benefit.

The Sponsor indicated that after performing the primary analysis on the ITT population using the One-to-one region algorithm, that in a small number of cases, adjacent anatomical regions were being mismatched by the strict one-to-one matching algorithm, therefore, the adjacent region algorithm was proposed. This type of analysis was introduced post-hoc. The details of the analysis and this reviewer's comments about the analysis can be found in study P829-34A results.

The primary efficacy endpoint was to determine the ability of Tc 99m P829 to correctly identify malignant lesions as confirmed by histopathology diagnosis. Below, the table 8 shows the sensitivity, specificity and agreement rate for each individual blinded read and the majority read. The majority read was a post hoc addition to the conduct of the study.

The Sponsor defined the majority read as a 2/3 majority from the three blinded readers therefore, if 2 out of 3 blinded readers indicated a positive results for a given region, the blinded majority read results would be positive. If the three individual blinded read results were positive, negative and indeterminate: positive, indeterminate and not assessed; or negative, positive and not assessed, then the blinded majority read result was considered indeterminate.

Sensitivity and Specificity: As seen in the table 8 below, the sensitivities and specificities for the individual blinded readers vary between reader and between algorithm. Between algorithms, it was seen that for all blinded readers, the adjacent region analysis resulted in increased sensitivity and decreased specificity values when compared to the one-to-one analysis. Thus, showing greater sensitivity using the adjacent region algorithm and greater specificity using the one-to-one algorithm. These results were expected because the adjacent region algorithm gives a greater opportunity to find agreement because a larger region is being assessed versus the single region which the one-to-one algorithm uses. The resulting decrease in sensitivity seen with the one-to one analysis is a result of a drop in the number of true positives identified by Tc-99m P829. Twelve cases were identified where the adjacent region resulted in a success and the one-to-one analysis resulted in a false negative.

Table 8. Primary Efficacy Results using the One-to-One and Adjacent Region Algorithms of the Diagnosis of the Main Presenting Lesion Relative to Histopathology

Reader	Algorithm	Parameter	Sens.	Spec.	Agreement	TP	TN	FP	FN	Total
Reader 1	Adjacent	Rates	79%	64.3%	77.2%	79	9	5	21	114
		Lower CI			69.7%					
	One to One	Rates	67.0%	85.7%	69.3%	67	12	2	33	114
		Lower CI			61.4%					
Reader 2	Adjacent	Rates	80.0%	50.0%	76.3%	80	7	7	20	114
		Lower CI			68.7%					
	One to One	Rates	70.0%	64.3%	69.3%	70	9	5	30	114
		Lower CI			61.4%					
Reader 3	Adjacent	Rates	88.0%	57.1%	84.2%	88	8	6	12	114
		Lower CI			77.3%					
	One to One	Rates	73.0%	78.6%	73.7%	73	11	3	27	114
		Lower CI			66.0%					
Majority Read	Adjacent	Rates	85.0%	57.0%	81.6%	85	8	6	15	114
		Lower CI			74.4%					
	One to One	Rates	71.0%	78.6%	71.9%	71	11	3	29	114
		Lower CI			64.1%					

Data Source: Supplemental Information submitted after filing, pg.019 Table 11-B(Letter Date 7/22/98)

Comment: The rationale for the Sponsor's decision to use the adjacent region algorithm appears reasonable. They identified that the blinded read localization of the lesion at times did not match the biopsy histopathology localization which was directed in most cases by the CT (either the surgeons review of the CT images or an actual CT guided biopsy).

Given the poor anatomical resolution seen with Nuclear imaging, the possibility that the blinded reader could have misidentified the actual location is possible. SPECT imaging does help in the localization process for nuclear imaging, however, it is still not as accurate as CT or biopsy. The only concern is the regions that the Sponsor identified as adjacent. These regions on paper appear too liberal, meaning a region anywhere in the left upper lobe of the lung on P829 could be counted as a success when compared to a lesion identified as left hilum by biopsy. There were 23 efficacy evaluable patients who had a change in agreement when the adjacent algorithm was employed.

The Sponsor reported a sensitivity and specificity for the investigator read as 97% and 57.1% respectively for the adjacent algorithm read. It was noted that a larger number of cases were found to be false negative by the blinded majority read as compared to these read as true positives by the Investigator. It is the Sponsors contention that reading Tc-99m P829 images with additional information provided by chest X-ray and CT facilitates accurate interpretation of a Tc99m P829 scan. Using the adjacent region algorithm, 12 false negative results were recorded in the blinded read for cases in which the investigator reported a true positive result. Three other cases were also found to be discordant by both investigator and blinded read. The Sponsor presented the individual cases that were identified as false negatives or diagnostically difficult in Vol. 1.67 pg. 069-071. The individual tumor types and blinded reads of for each of the cases can be found in Table 9. The factors the Sponsor identified that led to the difficulty in the image assessment were the following: 1) location of the lesion near a rib or the hilum; 2) size of the lesion (smaller lesions are more difficult to detect); 3) presence of diffuse Technetium Tc 99m P829 uptake in the diseased lung producing decreased target to background ratio; 4) presence of multiple lesions in the thorax that were not the target of the biopsy evaluation but were identified by the blinded readers; and 5) technical issues such as over-smoothing and poor reconstruction techniques by the site for images used in the blinded read.

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Table 9. Tumor and Blinded Read Demographics for False Negative Cases Reported for the Majority Read for both the Adjacent and One-to-One Region Algorithms

Patient Number	Region	Biopsy Result	Lesion Size	Tc99m P829 Read				CT Read			
				PI	BR1	BR2	BR3	PI	BR1	BR2	BR3
1-12	RH	Squamous	6 cm	–	–	–	–	–	+	IND	+
1-33	RUL	Adeno.	1cm	+	–	–	–	+	+	–	+
1-23	RML	Squamous	1.5 cm	–	–	–	–	–	ND	–	+
1-03	RUL	Adeno.	ND	+	–	–	–	+	+	–	+
1-28	RML	Adeno.	ND	–	–	–	–	–	+	–	–
8-01	RUL	Squamous	3 cm	+	–	–	–	+	+	–	+
8-06	RM	Adeno.	1.5 cm	+	–	–	–	–*	–*	IND*	–*
1-13	LLL	Adeno.	ND	+	ND	ND	ND	+	+	–	+
1-17	RUL	NSC	2 cm	+	–	–	–	+	+	+	+
4-03	RLL	Cancer	ND	+	–	–	–	+	+	+	+
5-15	LUL	Carcinoid	1 cm	–	–	–	–	+	+	IND	+
7-13	LUL	Adeno.	1 cm	+	–	–	–	+	+	+	+
8-02	RLL	Squamous	ND	+	–	–	+	+	+	+	+
8-03	RUL	Adeno.	1.5 cm	+	–	–	–	+	+	+	+
9-02	RLL	Carcinoid	2.5 cm	+	–	–	–	+	+	+	+

PI= site investigator, BR1,2,3=Blinded reader, *identified a lesion in the RUL, ND= not done, IND= Indeterminate, Data Source: Vol. 67, Table 11.0.0, pg.0194.

For the majority blinded read using the one-to-one algorithm, 29 cases were reported as false negative. Fifteen of these cases were reported in table 9 for the adjacent algorithm read. The remaining 14, which were not analyzed by the Sponsor are reported in table 10.

Comment: *Of the 15 cases reported to be false negative by majority blinded read for the adjacent algorithm, 4 were also read as negative by the investigator. This finding could be the result of Three problems: 1. Poor anatomic resolution provided by Nuclear Medicine imaging, or 2. The lesion biopsied was not the same lesion imaged or 3. Variability of Somatostatin receptor expression on the surface of the tumor. In 2 of the 4 cases, the majority CT read reported a lesion in the region of the main presenting lesion, therefore, the biopsy region should have been reported accurately. Of the 4 cases, case 1-12 was thought to be read negative due to location close to a rib, case 1-23 was thought to be read as negative due to diffuse uptake seen in the lungs, case 1-28 was though to be negative due to the presence of multiple alternate lesions and case 5-15 was though to be negative due to poor image quality.*

The discordance based on diffuse lung uptake should be investigated more carefully to identify if the affects of prior treatment(i.e. radiation or chemotherapy) may alter the normal biodistribution of Tc99m P829.

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Table 10. False Negative Cases for the Majority Blinded Read for One-to-One Algorithm Which Were Found to be Positive by Adjacent Region Algorithm

Patient Number	Region	Biopsy Result	Lesion Size	Tc99m P829 Read				CT Read			
				PI	BR1	BR2	BR3	PI	BR1	BR2	BR3
1-02	RLL	Squamous	4.0 cm	+ RUL	–	– RUL	– RML	+ RUL	+ RUL	+	– RUL
1-07	LUL	Non-small Cell	2.5 cm	+	– LLL	+ LLL	–	+	+	–	+
1-10	RUL	Small Cell	1.5 cm	+ RH	– RH	– RH	+	+	+	+	+
1-14	LUL	Adeno.	6.0 cm	+ LH	– LLL, LH	– LLL	+ LH	+	+ LH	+ LH	+ LH
1-15	RML	Squamous	7.5 cm	+	+ RLL	– RLL	– RLL	+	+	–	+
1-32	RUL	Non-small Cell	4.0 cm	+ RML	– RML	–	– RML	+	+	+	+
1-34	LUL	Non-small Cell	ND	+ LH	– LH	–	– LH	+ LH	ND LH	+ LH	+ LH
5-10	RML	Adeno.	NA	+ RUL	– RUL	– RUL	– RUL	+ RUL	IND	IND	– RUL
5-21	RLL	Squamous	2.2 cm	+	–	+ RH	– RH	+	+	+	–
5-34	LUL	Adeno.	0.5 cm	+	– LH	–	– LH	+	+ LH	+	+
7-03	RUL	Squamous	NA	– RH	– RH, RML	– RH, RML	– RH, RML	– RH	+ RH, RML	– RH	– RH, RML
8-22	LH	Squamous	NA	– LLL	– LLL	– LLL	– LLL	– LLL	+ LLL	+ LLL	+
16-01	LLL	Non-small Cell	4.0 cm	+	+	–	– LUL	+	ND	ND	ND
16-04	RUL	Adeno.	NA	+	– RML	– RML	– RML	+	+ RML	+	– RML

PI= site investigator, BR1,2,3=Blinded reader, ND= not done, IND= Indeterminate, Data Source: Vol. 67, Table 11.0.0, pg.0194, Appendix 16.2.10.3, Vol. 1.73.

Comment: *The regions identified below positive or negative signs for the blinded P829 readers in table 10 above, identify the region that made the read positive on adjacent algorithm. If these regions were positive on the CT read, the region was also identified on the table under the appropriate CT reader that read that region as positive.*

Several of the above lesions were large in size (greater than 2 cm) and should have been identified by the blinded reader if there was adequate tumor concentration of the drug.

Six cases were documented as false positive by the majority blinded read. In all six cases, uptake of Tc99m P829 appeared to occur in the presence of inflammation. There was agreement between the blinded majority read and the investigator read in five of the six cases that were false positive. One of the six blinded read cases was found to be negative by the investigator and an additional case (9-01) was found to be false positive by the investigator and not by the majority blinded read. The histopathology on this case was reported as fibrous tumor with granulomatous inflammation. The six cases identified as false positive by the majority blinded read are summarized in Table 11.

Table 11. Description of False Positive Cases from Blinded Read Efficacy Evaluable Data Set Using Adjacent Match Criteria to Histopathology

Patient	Blinded Read*	Investigator Read	Comment/Description
5-16	Positive	Positive	Uptake in lesion, chronic inflammation
5-17	Positive	Positive	Uptake in lesion, pathology sarcoidosis (granuloma)
5-27	Positive	Negative	Necrotizing granuloma, right upper lobe
8-07	Positive	Positive	Mixed inflammatory cell infiltrate, visualized in right lung field
8-11	Positive	Positive	Left lower lung field visualized by bronchiectasis and abscess formation
12-02	Positive	Positive	Right hilar lesion, acute and chronic fibrosis

Data Source: Sponsor Table 11-C, Vol. 67, page 072, * Majority blinded read.

Comment: Referring back to table 9, the false positives identified by the majority read vary from 2 to 7 in number for both algorithms together. The Analysis of the false negative cases shows that most patients, 4 patients each, fell under the following Sponsor, created categories: presence of alternate lesions, image quality and cases which need careful use of contrast to visualize. In many of these cases, it seems as though the drug is not localizing well enough to provide adequate target to background ratios so that the blinded readers could identify the abnormal uptake. Several of the lesions were reported as being larger then 1 cm. This size, and good uptake of the drug by the tumor, coupled with SPECT imaging, should have resulted in proper identification. One lesion was reported as 6 cm in size (patient 1-12) yet, 2 of the three blinded readers did not identify this lesion on the Tc99m P829 images. Poor concentration of the drug by the tumor would have to account for this false negative. The mechanism of uptake has been demonstrated by pre-clinical data, to be by somatostatin receptor binding. Thus, variability in somatostatin expression may account for the variability in Tcc9m P829 uptake.

The resultant uptake of Tc99m P829 by an inflammatory processes must be addressed for two reasons 1.) for those patients with biopsy prior to P829 imaging, did the inflammation caused by the biopsy procedure result in Tc99m P829 uptake or is the Tc99m P829 really binding to somatostatin receptors expressed on the surface of a malignant tumor, 2.) the exclusion criteria resulted in the exclusion of patients with active infections, therefore, this drug will have use in a limited population—it is recommended that the Sponsor do a study in a subset of patients with active inflammatory processes to help characterize uptake and look for potential differences in uptake seen with inflammation as opposed to malignancy (i.e. target to background ratios, pattern of uptake).

Agreement:

Agreement was defined by the Sponsor as whether or not the Technetium Tc99m P829 correctly identified the main presenting lesion in each patient as malignant or benign as confirmed by histopathology. Agreement rates were higher for the adjacent region algorithm than for the one to one algorithm. This is primarily due to the higher sensitivity seen for the adjacent algorithm. The rate of agreement was statistically significant for the majority blinded read for the adjacent region algorithm only (Table 12).

Table 12. P-Values for Rates of Agreements per blinded Reader and Algorithm

Read	One to One Algorithm P-value	Adjacent Algorithm P-value
Blinded Reader 1	0.605	0.058
Blinded Reader 2	0.605	0.085
Blinded Reader 3	0.225	0.001*
Majority Blinded Read	0.364	0.005*

***Significance at the 0.010 level. Data Source Vol.67, Tables 5.1.0,**

Interreader variability was assessed for the blinded readers using a kappa statistic. The results can be found in Table 13. The kappa statistic showed good agreement between readers for this study.

Table 13. Kappa Statistics for Blinded Read

Algorithm	Blinded Readers			
	1 vs. 2	1 vs. 3	2 vs. 3	Overall
One-to-One	0.699	0.679	.706	0.695
Adjacent	0.649	0.645	0.600	0.631

Data Source: Supplement submitted after filing dated 7/22/98, Table 11-D, pg. 021

Intent-to-Treat Population:
Efficacy analysis performed on the intent to treat population was very similar to the efficacy evaluable population results because the two populations only differed by two patients. The results will not be presented for this reason.

Secondary Efficacy Analysis:
Negative and Positive Predictive Values:
Using the calculated specificity and sensitivity results per blinded read and majority blinded read, negative and positive predictive values were graphically displayed for a wide range of disease prevalence. In cases where high prevalence exists, as was evidence by this trial, negative predictive values were found to be low. In cases were low prevalence existed, the negative predictive value was high, which is expected. For prevalences in between the high and low ends, it appears that this drug does not provide useful predictive information.

Solitary Pulmonary Nodule Subgroup Analysis:
The diagnosis of the main presenting lesion for Tc99m P829 relative to the histopathology results for three solitary pulmonary nodule subgroups was performed. The three SPN subgroups were defined as patients with SPN of 1-3cm in size, SPN of ≤ 6cm and all patients with SPN regardless of size. The sensitivity and specificity per blinded reader and per algorithm can be found in Tables 14-16. For all subgroups, specificity remained constant. Sensitivity appears to increases as size of the SPN increased. Sensitivity is lowest in the 1-3cm subgroups but steadily increases as the population with larger SPN are added. The Sponsor does not provide a Kappa statistic to assess interreader variability for this analysis. Both sensitivity and specificity values varied tremendously between readers within the same algorithm. Rates of agreement between the blinded read and histopathology were not statistically significant for either reader and algorithm

Comment: It is not clear from the study report or protocol, how the Sponsor defined solitary pulmonary nodule. In the strictest sense, it means no other regions are positive on a diagnostic test. For all those patients who were defined as presenting with a SPN, 22 out of 62 SPN patients had other areas read as positive on the site CT results reported in Table 11.0.0, Vol. 67. If the strict definition of SPN were to be applied, these patients should not have been included in SPN analysis. When this data was compared to the CT diagnosis as reported in the demographic data section, a majority of the patients enrolled had a diagnosis of a solitary mass or nodule, therefore, what criteria did the Sponsor use to finalize the diagnosis of SPN. Of the 62 patients defined as having a SPN at enrollment, 13 patients had reports of either adenopathy or multiple lesions reported on the CT diagnoses reported in the demographics section (Appendix 16.2.4.1, Vol. 1.70).

Table 14. Primary Efficacy Results using the One-to-One and Adjacent Region Algorithms of the Diagnosis of the Main Presenting Lesion Relative to Histopathology for all Patients with SPN

Reader	Algorithm	Parameter	Sens.	Spec.	Agree-ment	P value	TP	TN	FP	FN	Total
Reader 1	Adjacent	Rates	75.0%	83.3%	75.8%	0.195	42	5	1	14	62
		Lower CI			65.0%						
	One to One	Rates	64.3%	83.3%	66.1%	0.789	36	5	1	20	62
		Lower CI			54.9%						
Reader 2	Adjacent	Rates	76.8%	50.0%	74.2%	0.280	43	3	3	13	62
		Lower CI			63.3%						
	One to One	Rates	69.6%	50.0%	67.7%	0.701	39	3	3	17	62
		Lower CI			56.5%						
Reader 3	Adjacent	Rates	85.7%	66.7%	83.9%	0.012*	48	4	2	8	62
		Lower CI			73.9%						
	One to One	Rates	67.9%	83.3%	69.4%	0.598	38	5	1	18	62
		Lower CI			58.3%						
Majority Read	Adjacent	Rates	83.9%	66.7%	82.3%	0.025*	47	4	2	9	62
		Lower CI			72.1%						
	One to One	Rates	67.9%	83.3%	69.4%	0.598	38	5	1	18	62
		Lower CI			58.3%						

*Indicates significance at the 0.050 level.
Data Source: Supplemental Information submitted after filing, pg.022 Table 11-E1(Letter Date 7/22/98)

Table 15. Primary Efficacy Results using the One-to-One and Adjacent Region Algorithms of the Diagnosis of the Main Presenting Lesion Relative to Histopathology for all Patients with SPN 1-3 cm.

Reader	Algorithm	Parameter	Sens.	Spec.	Agree-ment	P Value	TP	TN	FP	FN	Total
Reader 1	Adjacent	Rates	59.3%	83.3%	63.6%	0.838	16	5	1	11	33
		Lower CI			47.8%						
	One to One	Rates	48.1%	83.3%	54.5%	0.983	13	5	1	14	33
		Lower CI			39.0%						
Reader 2	Adjacent	Rates	63.0%	50.0%	60.6%	0.914	17	3	3	10	33
		Lower CI			44.8%						
	One to One	Rates	59.3%	50.0%	57.6%	0.960	16	3	3	11	33
		Lower CI			42.0%						
Reader 3	Adjacent	Rates	74.1%	66.7%	72.7%	0.440	20	4	2	7	33
		Lower CI			57.0%						
	One to One	Rates	55.6%	83.3%	60.6%	0.914	15	5	1	12	33
		Lower CI			44.8%						
Majority Read	Adjacent	Rates	70.4%	66.7%	69.7%	0.590	19	4	2	8	33
		Lower CI			53.9%						
	One to One	Rates	55.6%	83.3%	60.6%	0.914	15	5	1	12	33
		Lower CI			44.8%						

Data Source: Supplemental Information submitted after filing, pg.023 Table 11-E2(Letter Date 7/22/98)

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Table 16. Primary Efficacy Results using the One-to-One and Adjacent Region Algorithms of the Diagnosis of the Main Presenting Lesion Relative to Histopathology for all Patients with SPN ≤ 6 cm.

Reader	Algorithm	Parameter	Sens.	Spec.	Agree-ment	P Value	TP	TN	FP	FN	Total
Reader 1	Adjacent	Rates	73.5%	83.3%	74.5%	0.278	36	5	1	13	55
		Lower CI			62.9%						
	One to One	Rates	63.3%	83.3%	65.5%	0.811	31	5	1	18	55
		Lower CI			53.5%						
Reader 2	Adjacent	Rates	73.5%	50.0%	70.9%	0.500	36	3	3	13	55
		Lower CI			59.1%						
	One to One	Rates	67.3%	50.0%	65.5%	0.811	33	3	3	16	55
		Lower CI			53.5%						
Reader 3	Adjacent	Rates	83.7%	66.7%	81.8%	0.039*	41	4	2	8	55
		Lower CI			70.8%						
	One to One	Rates	65.3%	83.3%	67.3%	0.722	32	5	1	17	55
		Lower CI			55.4%						
Majority Read	Adjacent	Rates	81.6%	66.7%	80.0%	0.071	40	4	2	9	55
		Lower CI			68.8%						
	One to One	Rates	65.3%	83.3%	67.3%	0.722	32	5	1	17	55
		Lower CI			55.4%						

*Indicates significance at the 0.050 level.
Data Source: Supplemental Information submitted after filing, pg.024 Table 11-E3(Letter Date 7/22/98)

Diagnosis of Main Presenting Lesion Relative to Histopathology Results using Computed Tomography

The Sponsor presented the majority blinded CT read data for the three algorithms per Subgroups compared to histopathology. The sensitivities and specificities for the majority blinded read for CT compared to Histopathology can be found in Table 17.

Table 17. Sensitivity and Specificity of Computed Tomography Compared to Histopathology for the Majority blinded read.

Algorithm	Population	Sens.	Spec.	TP	TN	FP	FN	Total
Adjacent	Efficacy Evaluable	96.0%	7.1%	96	1	13	4	114
	All SPN	94.6%	16.7%	53	1	5	3	62
	SPN 1-3cm	92.6%	16.7%	25	1	5	2	33
	SPN≤6cm	93.9%	16.7%	46	1	5	3	55
One to One	Efficacy Evaluable	88.0%	28.6%	88	4	10	12	114
	All SPN	91.1%	16.7%	51	1	5	5	62
	SPN 1-3cm	92.6%	16.7%	25	1	5	2	33
	SPN≤6cm	93.9%	16.7%	46	1	5	3	55

Data Source: Information submitted after filing, Letter Date 7/22/98

The Kappa statistics for the measurement of agreement between the blinded CT readers for the main presenting lesion using the adjacent region algorithm for the evaluable patient population are as follows: The agreement between CT blinded readers was poor to fair.

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	Kappa Statistic
Reader 1 vs. Reader 2	.387
Reader 1 vs. Reader 3	.558
Reader 2 vs. Reader 3	.303
Overall	.416

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As per the Sponsor, the blinded read results for all patients (adjacent region algorithm) showed that sensitivity of CT scans ranged from 88.0 to 98.0% among the three blind readers, with 96.0% sensitivity for the majority blind read. Specificity for CT scans was low and variable, with results of 0.0%, 21.4% and 7.1% for blind CT readers one, two and three, respectively, and with 7.1% specificity for the majority read. Agreement ranged from 79.8% to 86.8% for the three blind readers, with a majority agreement rate of 85.1%. The investigator read results for computed tomography showed sensitivity of 95.0%, specificity of 21.4%, and agreement of 86.0%.

Comparison of Sensitivity and Specificity of Technetium Tc 99m P829 and Computed Tomography for Main Presenting Lesion

Sensitivity for the CT scan majority blind read was 95.2% for all lesions, and 94.6%, 92.6% and 93.9% for all SPN, SPN between 1 and 3 cm, and SPN ≤6 cm. respectively; the corresponding sensitivities for Technetium Tc 99m P829 were 85.0% for all lesions, and 72.7%, 59.3% and 69.2% for all SPN, SPN between 1 and 3 cm, and SPN ≤6 cm. These differences in sensitivity were statistically significant at $p<0.05$ for all patients studied but not for all SPN subgroups studied. The differences between Technetium Tc 99m P829 and CT scan for specificity were more pronounced, with specificity for CT scan of 7.1% for all lesions, and 16.7% for each SPN subgroup, compared to Technetium Tc 99m P829 values of 57.1% for all lesions, and 66.7% for all SPN subgroups. These differences in specificity were statistically significant at $p<0.05$ for the main presenting lesion (all lesions) but not for any of the SPN subgroups. As seen in Table 18, the sample sizes for the SPN subgroups were small, therefore, any inferences drawn from the data must be looked at skeptically.

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Table 18. Comparison of Sensitivity and Specificity of Technetium Tc 99m P829 and Computed Tomography Majority Blind Read - Adjacent Region Algorithm Efficacy Evaluable Population

Population Image Type	TP	FN	Sensitivity	p-value	TN	FP	Specificity	p-value
Main Presenting Lesion (All Patients)								
Technetium Tc 99m P829	85	15	85.0%		8	6	57.1%	
Computed Tomography	96	4	95.2%	0.010	1	13	7.1%	0.046
SPN Subgroup (All SPN Patients)								
Technetium Tc 99m P829	47	9	83.9%		4	2	66.7%	
Computed Tomography	53	3	94.6%	0.077	1	5	16.7%	0.371
SPN Subgroup (1 to 3 cm Subgroup)								
Technetium Tc 99m P829	19	8	70.4%		4	2	66.7%	
Computed Tomography	25	2	92.6%	0.041	1	5	16.7%	0.371
SPN Subgroup (≤6 cm Subgroup)								
Technetium Tc 99m P829	40	9	81.6%		4	2	66.7%	
Computed Tomography	46	3	93.9%	0.077	1	5	16.7%	0.371
Data Source: Section 14.2, Tables 7.0.0, 7.0.1, 7.0.2, 7.0.3								

Data Source: Sponsor Table 11-F Vol. 67 page 081.

Diagnosis of Additional Lung Lesions Relative to Histopathology Results:

Fifteen patients had a total of 19 additional lesions biopsied. Of the 19 additional lesions, 16 were found to be positive for malignancy and 3 were found to be a benign process. The Sponsor provided sensitivity and specificity calculations for these 19 lesions by Tc99m P829 and CT blinded readers. This information can be found in Tables 19 and 20. The Sponsor does not identify this by algorithm. Again, the sample sizes for this group were extremely small and any inferences drawn from these tables should be done so with caution.

Table 19. Diagnosis of Additional Lesions Relative to Histopathologic Results For Tc 99m P829.

Reader	Sens.	Spec.	Agree-ment	P Value	TP	TN	FP	FN	Total
Reader 1	11/15 (73%)	1/4 (25%)	12/19 (63%)	0.816	11	1	3	4	19
Reader 2	11/15 (73%)	0/4 (0%)	11/19 (58%)	0.920	11	0	4	4	19
Reader 3	11/15 (73%)	0/4 (0%)	11/19 (58%)	0.920	11	0	4	4	19
Majority Read	11/15 (73%)	0/4 (0%)	11/19 (58%)	0.920	11	0	4	4	19

Data Source: Modification of Sponsor Table 9.1.0, Vol. 67, pg 0188.

Table 20. Diagnosis of Additional Lesions relative to Histopathologic Results For Computed Tomography.

Reader	Sens.	Spec.	Agree-ment	P Value	TP	TN	FP	FN	Total
Reader 1	7/15 (46%)	4/4 (100%)	11/19 (57.9%)	0.920	7	4	0	8	19
Reader 2	3/15 (20%)	4/4 (100%)	7/19 (36.8%)	1.00	3	4	0	12	19
Reader 3	11/15 (73%)	4/4 (100%)	15/19 (78.9%)	.274	11	4	0	4	19
Majority Read	7/15 (47%)	4/4 (100%)	11/19 (57.9%)	0.920	7	4	0	8	19

Data Source: Modification of Sponsor Table 9.1.0, Vol. 67, pg 0189.

Comment: It is not clear if the data reported in Tables 19 and 20 are for the one-to-one algorithm or adjacent algorithm.

Technetium Tc 99m P829 Blinded Read Derived Staging Results Compared to AJCC Staging Results for the Main Presenting Lesion for Patients with Primary Lung Cancer

There were 83 patients with a diagnosis of primary lung cancer based on the histopathologic information. The T, N, and M AJCC staging classifications and overall stage were based on the investigator determination, and the computer-generated stage for each blind Technetium Tc 99m P829 reader. Several patients (n=11)for whom the number of involved lymph nodes or presence/absence of distant metastases were recorded as NX or MX, respectively, indicating that one or both of these parameters were not assessed. Direct comparability to the results of the Technetium Tc 99m P829 staging procedure should not be performed in these cases. Of the remaining 72 evaluable cases, 20 patients (3.6%)had a match between the investigator staging and a majority blinded reader computer-generated staging. The majority of blinded read staging appeared to over-stage when compared to the investigator staging. This over staging could lead to inappropriate treatment.

The Sponsor did an analysis which found agreement rates of 63.0%, 54.4% and 74.7% for blinded readers 1, 2 and 3, respectively, where agreement for a given patient is considered to be a staging determination by the blind reader that is within one stage level of the AJCC classification.

Comment: This analysis was a post hoc addition to the protocol. The Sponsor's details regarding how this was to be performed can be found in Appendix B.

Examination of Demographic Subgroups

When reviewed for age, gender and race, the sensitivities for the majority blinded read per adjacent region algorithm were rather consistent. Specificity values were more variable due to small sample sizes within each subgroup. No meaningful conclusions could be drawn from these subgroup analyses.