Examination of Disease History Subgroups

Efficacy analyses on the main presenting lesion were conducted on two disease history subgroups of the efficacy evaluable population based on pre-injection renal and liver function, using the Adjacent Region algorithm. These two subgroups were defined as follows: for renal function subgroups, patients with BUN *or* creatinine > upper limit of the normal range at pre-injection (abnormal) versus patients with BUN *and* creatinine ≤ upper limit of the normal range at pre-injection (normal); for liver function subgroups, patients with AST, ALT, alkaline phosphatase, *or* LDH > upper limit of the normal range at pre-injection (abnormal) versus patients with AST, ALT, alkaline phosphatase, and LDH ≤ upper limit of the normal range at pre-injection (normal).

It should be noted that there were great differences in sample sizes between the renal function subgroup and the normal renal function subgroup; there were a total of 16 patients with abnormal baseline renal function compared to 95 normal patients. Therefore, it is difficult to draw meaningful conclusions from these efficacy data with such an imbalance in sample size.

Sensitivity was more than 80% for the blinded majority read and the investigator read regardless of baseline liver function status. Agreement was more than 80% for the blinded read and more than 92% for the investigator read in both subgroups. Specificity results were similar between the two liver function subgroups.

Binding Specificity of Technetium Tc99m P829 to Human Tumor Membranes

As per the Sponsor, biopsy samples were submitted for analysis but none of the specimens were usable in the assay.

Safety:

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

Extent of Exposure: A total of 142 patients received a single injection of Tc99m P829 in this study. The mean peptide, activity and volume levels administered can be found in Table 21. The radiochemical purity was >90% for all doses administered. The Lot used were: 9509B01D, 9509B02C & E, 9609B02F, G and H.

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Table 21. Exposure to the Study Agent

Dose Injected	Safety Population (N = 142)	Efficacy Population (N = 114)
P829 peptide (μg)		
Mean ± SE	42.7 ± 0.7	42.6 ± 0.8
Minimum, Maximum	20.0, 50.0	23.0, 50.0
Activity, Tc 99m (mCi)[1]		
Mean ± SE	19.2 ± 0.3	19.0 ± 0.3
Minimum, Maximum	12.3, 32.8	12.3, 32.8
Volume		
Mean ± SE	1.1 ± 0.0	1.2 ± 0.3
Minimum, Maximum	0.40, 2.3	0.46, 2.3
Data Source: Section 14.1, Tables 4.0.0, 4.1.0		

Data source: Sponsor Text Table 12-A, Vol. 1.67, page 093.

Adverse Events:

No deaths or serious adverse events were reported. No patients discontinued the study due to an adverse event. Of the 142 patients enrolled, 3 patients experienced a total of 5 adverse events. All 5 of the adverse events were considered "mild" in severity. Patient 12-05 received treatment for the adverse event, arthrosis, however, the Sponsor did not describe the treatment. All other adverse events resolved spontaneously. See Table 22 for a summary of the adverse events.

Table 22. Adverse Events

Patient	Adverse Event	Preferred Term	Time of Onset	Severity	Treatment Required	Relationship to study drug
7-02	Sore Throat	Pharyngitis	15 minutes	mild	No	Possibly Related
7-03	Wobbly	Abnormal Gait	6.5 hours	mild	No	Unrelated
	Tired	Fatigue		mild	No	Unrelated
12-05	Stiff knee	Arthrosis	21.5 hours	mild	Yes	Unrelated
	Specks of Blood with morning cough	Hemoptysis	21.5 hours	mild	No	Unrelated

Data Source Appendix 16.2.7.

Hematology Data:

Mean changes from the baseline value per post-injection timepoint can be found in Table 23. Of the parameters studied, statistically significant differences were reported for hematocrit (18-30 hrs.), hemoglobin (18-30hr.), neutrophil counts (2-4 hrs.), and lymphocyte counts (2-4 hrs.). Review of scatter plots which reported outliers that met the criteria of ± 70% of baseline, revealed that of the above parameters with statistically significant mean changes, only lymphocyte counts had outliers (n=8) reported. Of the 8 outliers, 7 were increases and 1 was a decrease from baseline.

Review of the shift tables revealed 7 patients that had decreases in hematocrit from normal to low, 2 patients that had increases in hemoglobin from normal to low, 6 and 11 patients had increases in neutrophils counts from normal to high per 2-4 hr. and 18-30 hr. respectively, and 7 and 13 patients had decreases in lymphocyte counts from normal to low for the 2-4 hr and 18-30hr. timepoints respectively.

Table 23. Hematology 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
Hematocrit (%)	n	129	127	122
	Mean	42.03	-0.21	-0.68
	p-value		0.546	0.024*
Hemoglobin (g/dL)	n	129	127	122
	Mean	13.51	-0.06	-0.16
	p-value		0.475	0.017*
RBC Count (10^6/mm^3)	n	129	127	122
	Mean	4.47	-0.01	-0.04
	p-value		0.506	0.108
WBC Count (10^3/mm^3)	n	129	127	122
	Mean	8.394	0.108	0.217
	p-value		0.079	0.057
Neutrophils (%)	n	129	127	122
	Mean	66.53	-0.91	0.36
	p-value		0.009**	0.421
Basophils (%)	n	129	127	122
	Mean	0.73	0	-0.03
	p-value		0.533	0.257
Eosinophils (%)	n	129	127	122
	Mean	1.80	0.02	-0.03
	p-value		0.669	0.395
Lymphocytes (%)	n	129	127	122
	Mean	23.97	1.23	-0.27
	p-value		<0.001**	0.343
Monocytes (%)	n	129	127	122
	Mean	6.93	-0.28	0.03
	p-value		0.052	0.998
Platelet Count (10^3/mm^3)	n	126	124	120
	Mean	272.6	-1.6	-2.7
	p-value		0.056	0.226

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.

Data Source: Sponsor Text Table 12-C, Vol. 1.67, page 098.

Table 24 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.

Table 24. Incidence of Treatment-Emergent Clinically Significant Hematology Values

Laboratory Test	Statistic	Post-Injection Evaluation Time	
		2-4 Hours	18-30 Hours
Hematocrit	CS/N (%) [Patient ID]	0/127	0/122
Hemoglobin	CS/N (%) [Patient ID]	0/127	2/122 (2%) [1-12, 1-15]
RBC Count	CS/N (%) [Patient ID]	0/127	1/122 (<1%) [1-12]
WBC Count	CS/N (%) [Patient ID]	1/127 (<1%) [7-11]	9/122 (7%) [1-03, 1-14, 1-15, 2-01, 5-10, 5-38, 7-11, 8-10, 8-24]
Platelet Count	CS/N (%) [Patient ID]	1/124 (<1%) [1-01]	3/120 (3%) [1-01, 1-03, 7-11]

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: Patient ID = patient identification number.

Data Source: Sponsor Text Table 12-E, Vol. 1.67, page 0103.

Of the two patient with changes in hemoglobin at the 18-30hr. timepoint, neither had baseline or 2-4 hour levels reported. Both patients were noted to have low hemoglobin levels at the 18-30hr time period. Of the 9 patients with changes in WBC counts at the 18-30 hr. timepoint, 3 patients had no baseline values to make a comparison, 5 patients had increases from baseline and one patient had a decrease from baseline. Of the 3 patients that had platelet count changes at the 18-30 hr. timepoint, all did not have baseline levels to compare the post-injection value.

Further review of the scatter plots for all parameters, outliers which met the criteria of ± 70% of the baseline can be found in Table 25.

Table 25. Number of Patients identified as Outliers for Hematology Parameters.

Parameter	2-4 hr.	18-30 hr.
Basophils	15	23
Eosinophils	18	21
Monocytes	2	7
Lymphocytes	8	7
WBC	0	1

Data Source: Additional Information submitted after filing, Letter date 7/24/1998 (timepoints are not mutually exclusive)

For those patients with basophil counts reported as outliers, all patients except one had values within the normal range. Of those with eosinophil counts reported as outliers, all but one patient had values within the normal range. Of those with outliers reported for monocyte counts, all but one patient had abnormal baseline values.

Clinical Chemistry: Mean changes from the baseline value per post-injection timepoint can be found in Table 26. Of the parameters studied, statistically significant differences were reported for alkaline phosphatase (2-4 hr and 18-30 hr.), total protein (18-30 hr.), LDH (18-30 hr.) total bilirubin (18-30 hr.), BUN (2-4 and 18-30hr.) and creatinine (2-4hr.).

Table 26. Clinical Chemistry Tests: Mean Changes from Pre-Injection Values

Laboratory Test	Statistic[1]	Pre-Injection Value	Change from Pre-Injection Value	
			2-4 Hours	18-30 Hours
Alkaline Phosphatase (U/L)	N	136	134	129
	Mean	105.0	-2.1	-2.0
	p-value		0.005**	0.020*
AST (U/L)	N	138	137	131
	Mean	23.9	-0.2	1.3
	p-value		0.363	0.396
ALT (U/L)	N	138	137	131
	Mean	25.9	-0.2	1.5
	p-value		0.571	0.661
Total Protein (g/dL)	n	138	137	131
	Mean	7.23	-0.02	-0.14
	p-value		0.428	<0.001**
Total Bilirubin (mg/dL)	N	138	137	131
	Mean	0.52	0.03	0.06
	p-value		0.076	0.024*
BUN (mg/dL)	N	138	137	131
	Mean	17.8	-0.5	0.5
	p-value		<0.001**	0.042*
Creatinine (mg/dL)	N	138	137	131
	Mean	0.91	-0.01	0.01
	p-value		0.045*	0.504
LDH (U/L)	N	135	132	125
	Mean	214.6	3.0	-9.8
	p-value		0.154	<0.001**

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.

Data Source: Sponsor Text Table 12-D, Vol. 1.67, page 099.

Shifts in clinical chemistry parameters were infrequent. Shifts per parameter and timepoint can be found in Table 27.

Table 27. Shift Table analysis

Parameter	2-6 Hr.	18-30 Hr.
Alkaline Phosphatase	1 increase	1 increase
	4 decreases	5 decreases
AST	3 increases	4 increases
	3decreases	2 decreases
ALT	6 increases	1 increase
	7 decreases	3 decreases
Total Bilirubin	3 increases	2 increases
		1 decrease
LDH	2 increases	
	5 decreases	7decreases
BUN		2 increases
	1 decrease	5 decreases
Creatinine		1 increase
	4 decreases	3 decreases

Data Source: Table 14.2.0, Vol. 1.68, page 015.

Those patients meeting the criteria for a clinically significant change in serum chemistry values are reported below. Table 28 represents those patients that had a clinically significant change which resulted in a laboratory value that was outside the normal range. Of the 2 patients with clinically significant changes in alkaline phosphatase, one patient was missing baseline data and the other had an abnormally high baseline level. Of the 6 patients with clinically significant changes in AST, all cases were noted to be increases in values with two patients having abnormally high baseline levels. Of the 5 patients with clinically significant ALT levels, 4 had abnormally increased baseline levels. Of the 3 patients with clinically significant total bilirubin levels, all were noted to be increases with one patient having an abnormally elevated baseline value. Of the 2 patients with clinically significant changes in LDH, all were noted to be increases with one patient (8-24) having a missing baseline value. Each case for BUN and creatinine was noted to be an elevation in values as compared to baseline.

Table 28. 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]	1/134 (<1%) [8-24]	2/129 (2%) [1-15, 8-24]
AST	CS/N (%) [Patient ID]	2/137 (1%) [8-08, 16-01]	4/131 (3%) [1-15, 5-12, 7-01, 8-24]
ALT	CS/N (%) [Patient ID]	0/137	5/131 (4%) [1-11, 1-15, 5-12, 7-01, 8-24]
Total protein	CS/N (%) [Patient ID]	0/137	0/131
Total bilirubin	CS/N (%) [Patient ID]	0/137	3/131 (2%) [1-11, 8-24, 16-05]
BUN	CS/N (%) [Patient ID]	0/137	1/131 (<1%) [8-19]
Creatinine	CS/N (%) [Patient ID]	0/137	1/131 (<1%) [8-23]
LDH	CS/N (%) [Patient ID]	3/132 (2%) [8-24, 12-03, 16-01]	1/125 (1%) [8-24]

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

Data Source: Sponsor Text Table 12-F, Vol. 1.67, page 0106.

Comment: Based on the Sponsor's definition of clinically significant changes, more patients were reported as having clinically significant changes in laboratory data, however, the Sponsor did not report them in the above table because the changes were found to result in values that were within the normal range. The actual numbers of patients with clinically significant laboratory changes are the following: AST- 15 patients, ALT- 7patients, total bilirubin- 26, LDH- 4 patients, BUN -4 patients and Creatinine -3 patients.

The Sponsor's explanation for those patients with clinically significant changes in serum chemistry values are as follows:

Tests of Liver Function (as per Sponsor)

AST values meeting the criteria for clinical significance were noted for 2 (1%) of 137 patients at 2-4 hours post-injection and 4 (3%) of 131 patients at 18-30 hours post-injection. Four patients (Patients 1-15, 5-12, 8-08, and 16-01) had normal AST values at pre-injection and high values at one post-injection assessment; none of these changes were considered attributable to Technetium Tc 99m P829. Two patients (Patients 7-01 and 8-24) had high AST values at pre-injection which increased further at post-injection assessments. For both patients, the abnormalities were judged by the investigators to be related to the patient's underlying diseases.

ALT values which met the criteria for clinical significance were noted for none of the 137 patients at 2-4 hours post-injection and for 5 (4%) of 131 patients at 18-30 hours post-injection. Four patients (Patients 1-11, 1-15, 7-01, and 8-24) had high pre-injection ALT values which were further elevated at 18-30 hours post-injection. Patient 5-12 had a normal pre-injection ALT (29 U/L) which increased to 50 U/L at 18-30 hours post-injection. None of the changes in ALT values were considered by the investigators to be attributable to Technetium Tc 99m P829.

Bilirubin values satisfying the criteria for clinical significance were noted for none of the 137 patients at 2-4 hours post-injection and for 3 (2%) of 131 patients at 18-30 hours post-injection. Two patients (Patients 1-11 and 8-24) with clinically significant changes had notable increases in bilirubin. Patient 8-24 had bilirubin values of 1.7, 1.5, and 7.4 mg/dL at pre-injection, 2-4 hours post-injection, and 18-30 hours post-injection, respectively. The investigator noted that this patient was admitted to the hospital for endoscopic retrograde cholangiopancreatography (ERCP) and removal of a stone from the biliary tree, and that the patient's elevated bilirubin and liver enzyme values normalized following this procedure. Patient 1-11 had values of 1.8, 1.8, and 2.5 mg/dL at pre-injection, 2-4 hours post-injection, and 18-30 hours post-injection, respectively; the elevated values were attributed to the patient's underlying disease, and no follow-up values are available. One patient (16-05) had a pre-injection value of 0.7 mg/dL with a value of 1.2 mg/dL (just outside the normal range) at the 18-30 hour assessment.

Other Enzymes (as per Sponsor)

Alkaline phosphatase (ALP) values meeting the criteria for clinical significance were noted for 1 (<1%) of 134 patients at 2-4 hours post-injection and 2 (2%) of 129 patients at 18-30 hours post-injection. Patient 1-15 had a high pre-injection ALP (133 U/L) which had increased to 168 U/L at 18-30 hours post-injection. Patient 8-24 had high ALP values at 2-4 hours post-injection (288 U/L) and 18-30 hours post-injection (359 U/L); no pre-injection value were available for comparison. None of these abnormal values or changes were considered by the investigators to be attributable to Technetium Tc 99m P829, and no follow-up testing was done.

LDH values satisfying the criteria for clinical significance were noted for 3 (2%) of 132 patients at 2-4 hours post-injection and 1 (1%) of 125 patients at 18-30 hours post-injection. Patient 12-03 had transient elevations in LDH at 2-4 hours post-injection, with a value that was just outside the upper limit of the normal range and had returned toward pre-injection values at 18-30 hours. Patient 16-01 had a normal pre-injection LDH which was >3X the upper limit of normal at 2-4 hours post-injection; no follow-up values are available. Patient 8-24 had high LDH values at 2-4 hours (253 U/L) and 18-30 hours (379 U/L) with no available pre-injection value; these elevations were attributed to the patient's pre-existing biliary disease. None of these changes were considered by the investigators to be attributable to Technetium Tc 99m P829.

Summary of Clinically Significant Laboratory Values (as per the Sponsor):
A total of 17 patients had one or more post-injection clinical laboratory result 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.
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 sign data from pre-injection values at each post-injection assessment are summarized in Table 29. Review of summary statistics for mean changes in vital signs revealed no clinically important trends, although some changes from pre-injection measurements for all parameters at various timepoints were statistically significant from baseline.

Table 29. 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)	73.9 ± 1.1	-1.5 ± 0.4**	-1.8 ± 0.5**	-2.3 ± 0.5**	-1.4 ± 0.5**	0.5 ± 0.7
SBP (mmHg)	135.0 ± 1.7	-1.2 ± 0.8	-1.8 ± 0.7*	0.0 ± 0.9	1.4 ± 1.0	0.2 ±1.2
DBP (mmHg)	77.1 ± 0.9	-0.5 ± 0.5	-0.8 ± 0.5	-0.3 ± 0.5	-0.5 ± 0.6	-1.8 ± 0.7*
Respiration (b/min)	18.4 ± 0.3	-0.1 ± 0.2	0.0 ± 0.2	-0.1 ± 0.2	0.1 ± 0.2	0.7 ± 0.2**
Temperature (°F)	97.2 ± 0.1	0.0 ± 0.0	-0.1 ± 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, Vol. 1.67, pg. 0109**

Seven patients had clinically significant changes in pulse. The Sponsor defined a clinically significant change as a change from baseline of ± 20bpm. Four of the 7 patients (8-5, 8-13, 8-24, and 15-4) had a clinically significant change at the 18-30 hour timepoint only. Of the remaining three patients, patient 2-2 had a clinically significant increase in pulse rate at the 30 minute (44→66bpm), 2-4 hr (44→64bpm)and 18-30 hour (44→65bpm)timepoints. This rise in pulse rate was accompanied by a rise in systolic pressure and a drop in diastolic pressure. This change was felt to be related to the study agent as per the investigator. Patient 8-2 had a clinically significant decrease in pulse at the 30 minute (100→80bpm) and 1 hour (100→78bpm)timepoints. This was accompanied by a drop in blood pressure and respiration rate, however, these changes were not clinically significant. Patient 16-1 had a clinically significant rise in pulse rate at the 2-4 hr. (64→84bpm) timepoint only, however, the 18-30 hr assessment was not collected. Pulse rate gradually rose in this patients with all other safety parameters appearing stable.

Four patients had clinically significant changes in systolic blood pressure. The Sponsor defined a clinically significant change as a change from baseline of ± 35mmHg. Two of the patients (7-7 and 8-9) had clinically significant drops in systolic blood pressure at the 18-30hour timepoint. In the case of patient 8-9, the baseline value had been elevated (184 mmHg), however, all other timepoints remained constantly elevated. In both cases, diastolic pressures also decreased but not to clinically significant levels. Patient 7-14 had a clinically significant increase in systolic blood pressure at the 1 hour (142→178mmHg) and 2-4 hour (144→180mmHg) timepoints. Diastolic pressure also increased but pulse and respiration rate remained stable. Patient 1-14 had a clinically significant increase in systolic pressure at the 2-4 hour timepoint (146→191mmHg). There was an accompanying slight rise in diastolic pressure but pulse and respiration rate remained relatively stable.

Two patients had clinically significant changes in diastolic pressures. The Sponsor defined a clinically significant change as a change from baseline of ± 25mmHg. Patient 8-9 had a drop in pressure at the 30 minute timepoint from a baseline of 94mmHg to a post-injection 30 minute value of 68mmHg. Systolic pressure was also seen to drop but not by a clinically significant amount.

Pulse and respiration rate remained stable. Patient 16-3 had an increase in diastolic pressure from a baseline of 60mmHg to a 5 minute value of 90mmHg and 1 hour value of 85mmHg. Systolic pressure increased as well, but pulse and respiration rate remained relatively stable.

Two patients had clinically significant changes in respiration rates. The Sponsor defined a clinically significant change as ± 10bpm. Patient 1-2 had an increase in respiratory rate at the 30 minute (20→30bpm) timepoint. Systolic and diastolic pressures were seen to increase slowly but not to clinically significant levels. Patient 1-23 had a clinically significant decrease in respiration rate at the 5 minute timepoint (32→20bpm). Systolic and diastolic pressures increased at this timepoint while pulse rate remained constant.

Comment: *The Sponsor did not provide a normal reference range for vital sign parameters and thus did not flag those baseline or post-injection values that were outside of normal range (not necessarily a clinically significant change). Mean change from baseline was the only summary statistic provided for this data other than the actual line listings. Review of the vital sign data did not show any clinically significant trends given the cut off points chosen by the Sponsor. These cut off points do not appear to be rigorous enough for an adequate safety assessment.*

Sponsor's Safety Conclusions:

A single intravenous injection of Tc99m 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 3 of the 142 patients experienced adverse events, and all events were judged to be of mild severity.

Changes in laboratory values over time were small in magnitude and were not clinically significant. Furthermore, for the most laboratory parameters, the numbers of patients with shifts form 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.

Reviewer's Discussion:

Safety: There were 5 adverse events reported in 3 patients. All adverse events were mild in severity. Only the adverse event, pharyngitis, had an onset within the first hour post-injection. The remaining adverse events were reported within the first 21 hours post-injection, however, they do not appear to be directly related to the study drug.

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 the18-30 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 in post-injection values when compared to baseline.

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. No scatter plots or shift table analysis was performed on the vital sign data. 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.

Execution/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 there presence suggests poor quality control during the conduct of the study. Several patients had violations that were not reported in the text portion of the study report by the Sponsor. Of the 114 patients with efficacy evaluable results, over 50% had biopsy prior to enrollment and thus prior to Tc99m P829 imaging. This violation may impact the efficacy analysis since biopsy prior to enrollment and thus prior to Tc99m P829 imaging could:

1.) Lead to the conscious or subconscious enrollment of patients with a particular tumor types that have a known propensity to express somatostatin receptors. 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, a relatively non-invasive procedure.

3.) Lead to a positive Tc99m P829 image due to inflammation resulting from the procedure. This issue would result in a larger number of falsely positive cases and thus a lower specificity. This finding was not seen.

Protocol deviations were reported in 30% of the patients, unfortunately, the actual deviations were not specified in the study report. For example, deviations in dose were reported as an injection of <13.5 mCi or >22.0mCI of Tc99m. The actual deviation for that individual patient was not specifically reported. The breakdown of patients per dose deviation and imaging time deviation should have been reported and if the numbers were found to be high, an analysis to see if dose variation had any effect on the efficacy results.

No in vitro receptor binding assays were performed on biopsied tissues obtained in this study. The Sponsor cites insufficient tissue to perform the assays.

The Sponsor's primary efficacy endpoint was 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, therefore, that is what was focused on in review of the study report results.

This study was driven by two primary sites of enrollment, site 1 providing 26% of the population and site 5 enrolling 25% of the population. The remainder of the population was distributed over 9 other sites. Both sites 1 and 5 were located in the United States.

The adjacent region algorithm analysis, which is what all the efficacy results were supported by, 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 negative one-to-one algorithm results which became positive on the adjacent region algorithm in 24 patients for all three blinded readers combined. Comparison of primary efficacy results per blinded reader and algorithm can be found in table 30.

Table 30. Primary Efficacy Data per Algorithm and Blinded Reader*

ALGORITHM AND READER	SENSITIVITY (%)	SPECIFICITY (%)	AGREEMENT (%)
Adjacent			
Reader 1	79	64	77
Reader 2	80	50	76
Reader 3	88	57	84
Majority	85	57	82
One-to-One			
Reader 1	67	86	69
Reader 2	70	64	69
Reader 3	73	79	74
Majority	71	79	72

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

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The sensitivity improved with the adjacent algorithm read but specificity improved with the one-to-one algorithm read. 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 in turn become positive for the adjacent region algorithm 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 there 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. With uncertainty regarding lesion localization, the one-to-one algorithm should be employed for purposes of the primary analysis.

Patients presenting with solitary pulmonary nodules were 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 identified 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. This finding suggests that the number of cases reported as SPN may not be accurate. The Sponsor will need to confirm these figures.

The results from the 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 was marked interreader variability seen for this analysis, however, the Sponsor did not do a kappa statistic to test for this. Given the earlier comments regarding the SPN definition applied and the marked interreader variability demonstrated here, these findings should not be referred to in labeling.

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.

7.0 Overview of Safety

Formulation:

Two formulations for the preparation of Tc99m P829 were used in the 14 clinical studies. The original formulation, designated as the investigational formulation, was modified in 1995 to improve radiochemical purity, as per the Sponsor. The original formulation was administered to 84 subjects/patients in three Phase 2 studies (829-00, 20 and 22). A total of 825 subjects/patients received the to-be-marketed formulation. Of those 825, 125 patients did not complete all specified protocol procedures. A change in dose preparation was also introduced during the course of the clinical trials. The modification was the introduction of a [redacted] step performed during the process of labeling the kit with Tc99m. The rationale for the introduction of this [redacted] The timing of the introduction of this preparatory step appeared to occur in September 1996. A list of clinical trials and the type of formulation and dose preparation used are listed in Table 1.

Table 1 Formulation and Dose preparation Method Per Study

Clinical Trial	Formulation
Phase 1	
829-10	Market Formulation
829-11	Market Formulation
829-12	Market Formulation
829-13	Market Formulation
Phase 2	
829-00	Investigational
829-20	Investigational
829-22	Investigational & Market
829-23	Market Formulation
829-30/IIa	Market Formulation
Phase 3	
829-30A	Market Formulation
829-30B	Market Formulation
829-32	Market Formulation
829-34A	Market Formulation
829-34B	Market Formulation

Data Source: Modification of Sponsor Table submitted in amendment (letter date 7/28/98)

Exposure:

A total of 909 subjects/patients received at least one intravenous injection of study drug. Of the 909 subjects/patients, 896 received a single injection and 14 patients received multiple injections. A breakdown of those patients receiving more than one intravenous administration can be found in Appendix D. Thus, a total of 923 injections of Tc99m P829 were administered. Of the 923 administered injections, 778 were administered in the United States and 145 were administered in Europe. Of the 923 administered injections, 914 were conducted using the radiolabeled peptide (9 subjects received unlabeled peptide in Study 829-13).

Of the 909 patients who received study drug, the vast majority (825 patients) received the to-be-marketed formulation. A total of 84 patients received the investigational formulation. Theses 84 patients were enrolled in three Phase 2 studies as follows: 23 patients in study 829-00, 43 patients in study P829-20 and 18 patients in study P829-22. Of the patients receiving the market formulation, approximately 80% received the [redacted] dose preparation and 20% received the [redacted] dose preparation.

Multiple Injections: Fourteen patients received multiple injections of study drug: 13 patients received 2 injections and 1 patient received 3 injections (829-22, 20, 30A, 32 and 34A). One additional patient received injections in both studies 829-34A and 829-22.

Comment: *The Sponsor gives no justification for the administration of the multiple injections and does not do a safety assessment on this subset of patients.*

In the majority of the cases where multiple injections were administered, it appears that the a significant amount of time elapsed between the initial dose and the repeated dose (weeks to months). The timing between injections is summarized in Appendix D. None of the patients who received multiple injections experienced any adverse events.

The peptide dose of 50μg was administered in 11 of the 14 clinical studies. In the remaining 3 studies, the dose of peptide administered ranged from 5-50μg (Studies 892-20, 22 and 23). The technetium Tc 99m dose ranged from 8-20 mCi for all clinical trials with the majority of trials administering between 15-20 mCi. For the pivotal studies (829-34 A & B), a peptide dose of 50μg and Tc99m dose of 15-20 mCi was planned to be administered. The Sponsor has summarized the overall extent of exposure in the following Table 2.

Table 2 Summary of Overall Extent of Exposure to Technetium Tc 99m P829[1] by Study Grouping

Variable:	Pivotal Phase 3 Studies[2] (N = 271)	All Phase 2 & 3 Studies (N = 854)	All Studies[1] (N = 923)
Dose of P829 (μg)			
N	271	834	892
Mean	43.4	35.5	36.1
Minimum, Maximum	18.3, 50.0	5.0, 87.0[3]	5.0, 87.0
Dose of Tc 99m, (mCi)			
N	270	848	907
Mean	19.5	17.8	17.5
Minimum, Maximum	12.3, 32.8	4.1, 32.8	4.1, 32.8

1 Includes 9 subjects enrolled in Study 829-13 who received unlabeled P829 peptide.
2 Includes Studies 34A & B in patients with suspicion of cancer in the lung.
3 Includes patients in Study 829-00 who received P829 from an *ad lib* preparation.
Source: Section 17, Tables 4.0.0 to 4.2.0

Data Source: Sponsor ISS, Vol. 1.84, Table 5

PRIOR AND CONCOMITANT MEDICATIONS

Other administered medications were captured for protocol-specified time points both prior to injection and following injection. Table 3 presents the most commonly administered types of medications (i.e. those prior and concomitant medications administered to 10% or more of patients) within a WHO therapeutic classification system for the pooled data.

Table 3. Most Common[1] Prior and Concomitant Medications By WHO Therapeutic Classification and Study Grouping

WHO Therapeutic Classification:	Pivotal Phase 3 Studies[2] (N = 271)	All Phase 2 & 3 Studies (N = 854)
Patients Reporting at Least One Prior or Concomitant Medication[1]	237 (87%)	659 (77%)
Stomatologic Preparations	68 (25%)	117 (14%)
Calcium Channel Blockers	65 (24%)	126 (15%)
Diuretics	62 (23%)	132 (15%)
Analgesics	54 (20%)	145 (17%)
Antacids, Drugs for Peptic Ulcer and Flatulence	49 (18%)	155 (18%)
Psycholeptics	49 (18%)	111 (13%)
Mineral Supplements	44 (16%)	85 (10%)
Anti-Asthmatics	43 (16%)	70 (8%)
Agents Acting on Renin-Angiotensin System	42 (15%)	97 (11%)
Nasal Preparations	41 (15%)	58 (7%)
Psychoanaleptics	38 (14%)	81 (9%)
Sex Hormones and Modulators of the Genital System	38 (14%)	101 (12%)
Cardiac Therapy	37 (14%)	82 (10%)
Serum Lipid Reducing Agents	36 (13%)	86 (10%)
Drugs Used in Diabetes	35 (13%)	88 (10%)
Beta-Blocking Agents	32 (12%)	90 (11%)
Vitamins	27 (10%)	60 (7%)
Thyroid Preparations	20 (7%)	84 (10%)

1 Reported by 10% or more of patients in either Study Grouping.
2 Includes Studies 829-34A & B in patients with suspicion of cancer in the lung.
Source: Section 17, Tables 5.0.0 and 5.1.0

Data Source: Sponsor ISS, Vol. 1.84, Table 7

The most commonly administered individual medications in both the Phase 3 studies and the Phase 2 & 3 studies combined was acetylsalicylic acid (18% and 9% of patients, respectively). Use of concomitant medications was restricted during conduct of the four Phase 1 studies. Of the 69 patients enrolled in these studies, 58 were normal healthy volunteers; concomitant medication use in these patients was infrequent and usually involved the administration of contraceptives, analgesics and vitamin and mineral supplements.

Safety Data Collection:

Safety data was collected at various time points throughout the course of the 14 clinical studies. The type of safety parameters monitored also varied across the 14 clinical studies. The type of safety parameters monitored per study is shown in table 4. The individual parameters studied per safety category can be found in Appendix E.

Table 4. Safety Parameters Collected Per Study

Study Number	Phase	Adverse Events	Vital Signs	Urinalysis	Hematology	Complete Chemistry Panel	Abbreviated Chemistry Panel*	Immunogenicity
P829-10	1	X	X	X	X	X		
P829-11	1	X	X	X	X		X	
P829-12	1	X	X	X	X	X		X
P829-13	1	X	X	X	X	X		X
P829-00	2	X						
P829-20	2	X	X					
P829-22	2	X	X	X	X	X		
P829-23	2	X	X	X	X	X		
P829-30IIa	2	X						
P829-30A	3	X	X		X		X	
P829-30B	3	X	X		X		X	
P829-32	3	X	X		X		X	
P829-34A	3	X	X		X		X	
P829-34B	3	X	X		X		X	

This panel includes only the following: SGOT, SGPT, Alk. Phos, LDH, t bili, t Protein, BUN, Cr.
Data Source: Protocols per individual study

As seen in Table 4, 2 clinical studies (829-00 and 30IIa) only collected adverse events as the primary measure of safety (N=36). Urinalysis data was collected in 6 studies, all of which used the to-be-marketed formulation. Serum chemistry parameters were studied in 12 of the 14 clinical studies, however, an abbreviated serum chemistry panel was studied for all the Phase 3 studies. A complete chemistry panel was assessed in 5 clinical studies. Please refer to Appendix E for the definition of what parameters were studied in the abbreviated and complete chemistry panels. Two studies performed immunogenicity testing and one study performed glucose tolerance testing.

Adverse Events:

Adverse event reporting was performed in all 14 clinical studies. Adverse events were to be captured up to 24 hours post-injection for all five Phase 3 studies, in all four Phase 1 studies and in one Phase 2 study (n=704). Out of the remaining 4 studies, adverse events were monitored up to 4 hours post-injection for one study (829-30IIa) and at undesignated times up to 2 hours post-injection for the remaining 3 studies.

All adverse events were coded using the WHO Adverse Reaction Terminology (WHOART) dictionary. Tabular summaries of the incidence of treatment-emergent adverse events are presented by WHOART body system and preferred term. An adverse event was considered to be treatment-emergent if the adverse event began after injection with technetium Tc 99m P829 or if the event was present at baseline and worsened in severity after injection. If an adverse event was reported more than once, the greatest known severity and the closest known relationship to the study agent was presented. The severity categories of mild, moderate and severe were included in the case report form (CRF) across all 14 studies and are used in the integrated summary of safety (ISS) for tabulation. Because the case report forms, for several of the studies, used different relationship categories, relationship of the event to the study agent was collapsed by the Sponsor into three categories as follows for tabulation in the ISS:

ISS Category:	CRF Categories:
Not related	Unrelated Not related (Study Agent) Not given prior to AE
Probably not related	Probably not related Probably unrelated
Related	Related Possibly related Probably related

A total of 49 (5%) subjects/patients reported 65 adverse events. Sixty-three adverse events were reported in the United States studies and 2 adverse events were reported in the European studies. No deaths or serious adverse events were reported and no patients discontinued participation in any of the clinical studies due to an adverse event. Table 5 presents the adverse events by body system and geographic region.

Comment: *The Sponsor reported the occurrence of adverse events per total number of injections of study drug rather than per total number of patients.*

Table 5. Incidence of Treatment Emergent Adverse Events by Body System and Geographic Region

Body System/ Preferred Term	United States n (%)	Europe n (%)
Total Number of Patients	765	146
Total Number of Injections	778	145
Total Number of Patients with an AE	47 (6)	2 (1)
CNS and PNS System	16 (2)	0
Headache	9 (1)	0
Dizziness	5 (<1)	0
Cramps, legs	1 (<1)	0
Gait Abnormal	1 (<1)	0
Hypertonia	1 (<1)	0
Hypoaesthesia	1 (<1)	0
Gastrointestinal System	15 (2)	0
Nausea	8 (1)	0
Diarrhea	6 (<1)	0
Vomiting	3 (<1)	0
Abdominal Pain	2 (<1)	0
Dyspepsia	1 (<1)	0
Glossitis	1 (<1)	0
Tooth Ache	1 (<1)	0
Body As A Whole	13 (2)	0
Back Pain	4 (<1)	0
Fatigue	4 (<1)	0
Chest Pain	2 (<1)	0
Abdomen enlarged	1 (<1)	0
Malaise	1 (<1)	0
Pain	1 (<1)	0
Rigors	1 (<1)	0
Syncope	1 (<1)	0
Vascular (extracardiac) Disorders	4 (<1)	0
Flushing	1(<1)	0
Vasodilatation	3(<1)	0
Respiratory System	3 (<1)	0
Dyspnea	1 (<1)	0
Hemoptysis	1 (<1)	0
Pharyngitits	1 (<1)	0
Special Senses	3 (<1)	0
Taste Perversion	3 (<1)	0
Cardiovascular Disorders	1 (<1)	0
Hypertension	1 (<1)	0
Endocrine Disoreders	0	1 (<1)
Endocrine Disorder NOS	0	1 (<1)
Musculoskeletal	1 (<1)	0
Arthrosis	1 (<1)	0
Platelet, Bleeding/Clotting Disorder	1 (<1)	0
Epistaxis	1 (<1)	0
Psychiatric Disorder	1 (<1)	0
Somnolence	1 (<1)	0
Resistance Mechanism Disorder	1 (<1)	0
Infection	1 (<1)	0
Skin and Appendages	1 (<1)	0
Sweating Increased	1 (<1)	0
Vision Disorder	1 (<1)	0
Eye Abnormality	1 (<1)	0
White Cell And RES Disorder	0	1 (<1)
Lymphocytosis	0	1 (<1)
Application Site Disorder	1 (<1)	0
Injection site pain	1 (<1)	0

Data Source: ISS, Vol. 1.84, Table 6.6.0. Note: Patients reporting a particular adverse event more than once are only counted once within each body system and preferred term. Table includes multiple observations for patients enrolled more than once.

No single WHOART body system had more than 2% of the total injections resulting in an adverse event. The 2 body systems with the most adverse events reported were the central and peripheral nervous system and the gastrointestinal system. Headache and nausea were the two most commonly reported adverse events occurring in 1% of the studied population. Other commonly reported adverse events occurring in these two body systems include dizziness and diarrhea. Incidence of adverse events by severity and relationship to study drug can be found in Table 6.

Table 6. Incidence of Adverse Events by Severity and Relationship To Study Drug.

Body System/Preferred Term	Mild n	Moderate n	Severe n	Not Related n	Probably Not Related n	Related n
CNS and PNS System	12	3	1	3	7	6
Headache	6	2	1	1	3	5
Dizziness	5	0	0	0	3	2
Cramps, legs	1	0	0	1	0	0
Gait Abnormal	1	0	0	1	0	0
Hypertonia	0	1	0	0	1	0
Hypoaesthesia	1	0	0	1	0	0
Gastrointestinal System	11	2	2	1	8	6
Nausea	7	1	0	0	3	5
Diarrhea	4	1	1	1	4	1
Vomiting	2	1	0	0	3	0
Abdominal Pain	0	1	1	0	2	0
Dyspepsia	1	0	0	0	0	1
Glossitis	1	0	0	0	0	1
Tooth Ache	0	0	1	0	1	0
Body As A Whole	10	0	2	5	7	1
Back Pain	2	0	2	2	2	0
Fatigue	4	0	0	1	2	1
Chest Pain	1	0	0	0	2	0
Abdomen enlarged	1	0	0	0	1	0
Malaise	1	0	0	1	0	0
Pain	0	0	1	0	1	0
Rigors	1	0	0	1	0	0
Syncope	1	0	0	1	0	0
Vascular Disorders	4	0	0	0	1	2
Flushing	3	0	0			
Vasodilatation	1	0	0	0	1	2
Respiratory System	3	0	0	1	1	1
Dyspnea	1	0	0	0	1	0
Hemoptysis	1	0	0	1	0	0
Pharyngitits	1	0	0	0	0	1
Special Senses	2	0	0	1	1	1
Taste Perversion	2	0	0	1	1	1
Cardiovascular Disorders	1	0	0	0	1	0
Hypertension	1	0	0	0	1	0
Endocrine Disorders	1	0	0	0	1	0
Endocrine Disorder NOS	1	0	0	0	1	0
Metabolic/Nutritional	1	0	0	1	0	0
Weight Decrease	1	0	0	1	0	0
Musculoskeletal	1	0	0	1	0	0
Arthrosis	1	0	0	1	0	0

Data Source: ISS , Vol. 1.84, Tables 6.7.0 & 6.8.0

Table 6. Con't.

Body System/Preferred Term	Mild n	Moderate n	Severe n	Not Related n	Probably Not Related n	Related n
Platelet, Bleeding/Clotting Disorder	1	0	**0**	0	1	**0**
Epistaxis	1	0	**0**	0	1	**0**
Psychiatric Disorder	1	0	**0**	0	0	**1**
Somnolence	1	0	**0**	0	0	**1**
Resistance Mechanism Disorder	1	0	**0**	0	1	**0**
Infection	1	0	**0**	0	1	**0**
Skin and Appendages	1	0	**0**	1	0	**0**
Sweating Increased	1	0	**0**	1	0	**0**
Vision Disorder	0	1	**0**	1	0	**0**
Eye Abnormality	0	1	**0**	1	0	**0**
White Cell And RES Disorder	1	0	**0**	0	1	**0**
Lymphocytosis	1	0	**0**	0	1	**0**
Application Site Disorder	1	0	**0**	1	0	**0**
Injection site pain	1	0	**0**	1	0	**0**

Data Source: ISS, Vol. 1.84, Tables 6.7.0 & 6.8.0

The majority of the adverse events were reported as mild to moderate in severity with a total of 7 adverse events rated as severe in 4 patients. A brief summary of each patients who experienced a severe adverse event is listed below:

Patient 30A-1-5: This patient experienced severe abdominal pain and diarrhea approximately 18 hours post-injection. Symptoms lasted for 2 hours and resolved spontaneously. No treatment was administered and the investigator felt these symptoms were probably not related to the study drug.

Comment: Time of onset does not suggest a direct relationship between the adverse event and the test drug. The patients laboratory data appeared relatively stable. The 24 hour vital sign assessment was also stable. This patient received the unheated, to-be-marketed formulation.

Patient 30A-4-2: This patients experienced severe tooth pain approximately 23 minutes post-injection. The pain lasted for 5 minutes and resolved without treatment. The investigator felt that this was probably not related to the study drug.

Comment: Given the time of onset, this may or may not be related to the study drug. However, there is no other evidence to support a direct relationship between the adverse event and the test drug. All vital signs were stable before and after this adverse event. The patient received the unheated, to-be-marketed formulation.

Patient 11-1-1: This patient experienced severe backpain, headache and lower extremity pain. The onset of headache pain began approximately 1 hour post-injection and the back and leg pain began approximately 4 hours post-injection. The headache pain was felt to be related to the study drug while the back and leg pain were felt to be probably not related.

Patient 11-1-2: This patient experienced severe back pain approximately 4 hours post-injection. The pain was self-limiting and felt to be probably not related to the study drug by the investigator.

Comment: *The back and leg pain experience by patients 11-1-1 and 11-1-2 were probably related to the imaging procedure rather than the study drug. Imaging for this study was scheduled to occur at 1 hour and between 3-6 hours post-drug administration. Patients were required to lie on there back for the imaging procedure. Patient 11-1-1 had stable vital signs until the 3-6 hour assessment when a rise in systolic and diastolic pressure was noted. Pulse and respiratory rate were stable. Vital signs for patient 11-1-2 were stable for all times of assessment. Both patients 11-1-1 and 11-1-2 received the unheated, to-be-marketed formulation.*

The majority of the patients received the proposed for market formulation (825 patients, 838 injection). Table 7 below presents the most commonly occurring treatment emergent adverse events reported over all studies by formulation.

Table 7. Incidence of Most Common[1] Treatment-Emergent Adverse Events By WHOART Preferred Term and Formulation (Patient Population: All Studies)

	Number (%) of Patients		
		Formulation	
WHOART Preferred Term:	Total (N* = 923)	Proposed for Market (N* = 838)	Investigational (N* = 85)
Patients With at Least One Adverse Event[2]	49 (5%)	46 (5%)	3 (4%)
Headache	9 (<1%)	9 (1%)	0 (0%)
Nausea	8 (<1%)	7 (<1%)	1 (1%)
Diarrhea	6 (<1%)	5 (<1%)	1 (1%)
Dizziness	5 (<1%)	5 (<1%)	0 (0%)
Back Pain	4 (<1%)	4 (<1%)	0 (0%)
Fatigue	4 (<1%)	4 (<1%)	0 (0%)
Vomiting	3 (<1%)	3 (<1%)	0 (0%)
Flushing	3 (<1%)	3 (<1%)	0 (0%)
Taste Perversion	3 (<1%)	3 (<1%)	0 (0%)
Abdominal Pain	2 (<1%)	2 (<1%)	0 (0%)
Chest Pain	2 (<1%)	2 (<1%)	0 (0%)

1 Events reported by two or more patients overall.
2 Patients with more than one adverse event are tabulated only once.
Source: Section 17, Table 6.9.0

N* = number of drug administrations. Data Source: Sponsor ISS, Vol. 1.84, Table 11.

Demographics:
The incidence of adverse events by demographic characteristics can be found in Table 8 below.

Table 8. Overall Incidence of Adverse Events by Study Grouping and Demographic Factor

Demographic Factor:	Number (%) of Patients	
	Pivotal Phase 3 Studies[1] (N = 271)	All Studies (N = 923)[2]
Patients Reporting at Least One Adverse Event[3]	11/271 (4%)	49/923 (5%)
Age (years)		
< 65	6/124 (5%)	37/598 (6%)
≥ 65	5/147 (3%)	12/324 (4%)
Gender		
Male	7/168 (4%)	22/497 (4%)
Female	4/103 (4%)	27/426 (6%)
Weight		
< Median	6/131 (5%)	24/449 (5%)
≥ Median	5/140 (4%)	24/456 (5%)
Race		
Caucasian	10/215 (5%)	33/727 (5%)
Non-Caucasian	1/56 (2%)	13/166 (8%)

1 Includes Studies 829-34A & B in patients with suspicion of cancer in the lung
2 Age, weight and race were not reported in 1, 18 and 30 patients, respectively.
3 Patients with more than one adverse event are tabulated only once.
Source: Section 17, Tables 6.11.0 to 6.18.0

Data Source: Sponsor ISS, Vol. 1.84, Table 12

A slightly higher proportion of patients under 65 years of age reported adverse events as compared to patients over 65 years. Complaints involving the CNS & PNS and GI systems appear to account for the slight differences. Gender reveals a slight increase in reporting of adverse events in females. These differences again fall in the CNS and GI body systems categories. In particular, females reported a higher incidence of dizziness and diarrhea. No major differences were seen across all studies by patient weight. A higher incidence of adverse events was seen in the Caucasian vs. the non-Caucasian group.

Comment: *Review of the pharmacokinetic data revealed a potential gender difference in renal clearance of the study agent. In the small sample size, men were found to have a higher renal clearance rate when compared to women. The small sample size and variation seen within the data would lead this reviewer to suggest that further studies be performed to either confirm this analysis or refute it. Since the major route of elimination was not identified by the Sponsor and given the slight gender effect seen in renal clearance, all safety data should be analyzed by gender.*

Vital Signs:

Vital sign parameters collected included systolic and diastolic blood pressure, pulse, respiration rate and temperature. Two clinical studies did not collect vital sign data (829-30IIa and 00).

Of the 12 clinical studies remaining, 2 did not collect temperature data (829-30A & B). The Sponsor presented the mean changes from baseline for all the Phase 2 and 3 studies together. Phase 1 data was presented separately. Collection time points were collapsed by the Sponsor for purposes of pooling the data into the following time points: 5-15 minutes, 30 minutes, 1 hour, 1.5-6 hours, and 18-30 hours post-injection.

The mean changes from baseline from pre-injection to post-injection time point for all Phase 2 and 3 studies can be found in the Table 9. Mean systolic and diastolic blood pressures decreased from pre-injection values, approximately 1 to 2 mmHg at most assessment times; similar results were observed for mean pulse which decreased by 1 to 2 beats/minute at most time points. Changes in mean respiratory rate were small with decreases of 0.1 to 0.2 breaths/minutes reported at most assessments. Mean changes from baseline were not presented for the Phase 1 studies.

Table 9. Summary of Vital Signs Changes (Mean ± SE) from Pre-Injection to Each Post-Injection Evaluation (Population: All Phase 2 and 3 Studies[1])

Vital Sign:	Pre-Injection (N = 759)	Change to Post-Injection Evaluation: 5 - 15 min. (N = 753)	30 min. (N = 742)	1 hr. (N = 587)	1.5 - 6 hr. (N = 740)	18 - 30 hr. (N = 508)
Pulse, bpm	74.6 ± 0.5	-1.5 ± 0.2	-2.2 ± 0.2	-2.4 ± 0.3	-1.5 ± 0.3	-0.3 ± 0.4
Systolic BP, mmHg	130.7 ± 0.7	-1.5 ± 0.3	-2.1 ± 0.3	-1.7 ± 0.4	-0.4 ± 0.4	-2.5 ± 0.6
Diastolic BP, mmHg	78.0 ± 0.4	-0.8 ± 0.2	-0.9 ± 0.2	-0.8 ± 0.3	-0.7 ± 0.3	-2.0 ± 0.4
Respiration, breaths/min	18.6 ± 0.2	-0.2 ± 0.1	-0.3 ± 0.1	-0.2 ± 0.1	-0.1 ± 0.1	0.2 ± 0.1

[1] Reported Ns are for Systolic Blood Pressure; other Ns were slightly lower, See Table 9.1.0
Source: Section 17, Table 9.1.0

Data Source: Sponsor ISS, Vol. 1.84, Table 21

The Sponsor designated clinically significant changes in vital sign values when post injection levels met the following criteria when compared to baseline.

Vital Sign:	Clinically Significant Change:
Systolic blood pressure	+/- 35 mmHg
Diastolic blood pressure	+/- 25 mmHg
Pulse rate	+/- 20 beats/minute
Respiration rate	+/- 10 breaths/minute

Comment: These cut off points, particularly those for blood pressure, afford a wide range of variability to exist within the data. It is often recommended to Sponsors to use a cut off point of a change in 20 mmHg and 10 mmHg be used for systolic and diastolic pressures respectively. Review of the adverse event profile does not suggest any direct safety implication (findings such as syncopal episodes etc.) corresponding to vital sign data that would warrant a reanalysis of the data . Those patients experiencing headache, dizziness, flushing did not show any significant changes in vital sign parameters.

The number of clinically significant changes reported for the Phase 2 and 3 studies can be found in the Table 10.

Table 10. Incidence of Clinically Significant Changes in Vital Signs from Pre-Injection to Each Post-Injection Evaluation (Population: All Phase 2 & 3 Studies)

Vital Sign Change	Clinically Significant Change to Post-Injection Evaluation:				
	5 – 15 min.	30 min.	60 min.	1.5 - 6 hr.	18 - 30 hr.
Pulse, bpm					
≤ -20	3/753 (<1%)	13/741 (2%)	13/587 (2%)	10/739 (1%)	10/508 (2%)
≥ +20	3/753 (<1%)	4/741 (<1%)	0/587 (0%)	6/739 (<1%)	8/508 (2%)
Systolic BP, mmHg					
≤ -35	2/753 (<1%)	4/742 (<1%)	1/587 (<1%)	5/740 (<1%)	8/508 (2%)
≥ +35	0/753 (0%)	0/742 (0%)	2/587 (<1%)	7/740 (<1%)	2/508 (<1%)
Diastolic BP, mmHg					
≤ -25	0/753 (0%)	4/742 (<1%)	2/587 (<1%)	4/739 (<1%)	3/508 (<1%)
≥ +25	1/753 (<1%)	1/742 (<1%)	3/587 (<1%)	3/739 (<1%)	1/508 (<1%)
Respiration, breaths/min					
≤ -10	1/722 (<1%)	1/711 (<1%)	1/587 (<1%)	2/709 (<1%)	1/505 (<1%)
≥ +10	0/722 (0%)	3/711 (<1%)	1/587 (<1%)	2/709 (<1%)	1/505 (<1%)

Source: Secuon 17, Table 9.3.0

Data Source: Sponsor ISS, Vol. 1.84, Table 23.

Changes were most commonly reported for pulse with both increases and decreases of 20 beats/minute reported across the post-injection time points but consistently showing a trend in decreasing pulse levels post-injection for all time points except the 5-15 minute time point. Clinically significant changes in systolic and diastolic blood pressure and respiratory rate were reported in 1% or fewer of patients at all but one evaluation timepoint; 2% of all patients (8 of 508 patients) had a decrease in systolic blood pressure of 35 mmHg relative to pre-injection values at the 18 to 30 hour assessment. Those clinically significant changes deemed noteworthy by the Sponsor are described in below. The Sponsor did not attribute any of the changes to the administration of the study drug.

Patient 30A-01-04 was a 56 year-old male with underlying gastrointestinal carcinoid; the patient was receiving Sandostatin® therapy. The patient's baseline systolic blood pressure (SBP) was 120 mmHg and respiratory rate was 10 breaths/minute; at the 1.5 to 6 hour assessment the SBP had increased to 186 mmHg and respiration to 32 breaths/minute. Both changes met the definition of a clinically significant change. The vital signs parameters had returned toward baseline by the 18 to 30 hour assessment. The investigator attributed the changes to underlying hypertension and exertion.

Reviewer's Comment: *Diastolic pressure increased form a baseline value of 80mmHg to 98mmHg at the 3-6 hour assessment. Pulse was also noted to increase from a baseline value of 64 to 72bpm. All laboratory values appeared relatively stable. Therefore the investigator's assessment appears sound.*

Patient 30A-06-01 was a 30 year-old female with suspected gastrointestinal carcinoid. The patient had resting tachypnea with a respiratory rate of 24 breaths/minute at baseline; at the 30 minute and 1.5 to 6 hour assessments respiratory rate met the criteria for clinically significantly increases from baseline with values of 40 and 36 breaths/minute, respectively.

Respiratory rate had returned to the baseline value by the 18 to 30 hour assessment. The patient tolerated study procedures well; the accuracy of the recorded vital signs values were questioned by the investigator.

Reviewer's Comment: *Blood pressure assessments appeared stable during this time however, pulse rate was noted to increase from a baseline of 93bpm to 106bpm at the 3-6 hour assessment. All laboratory values appeared stable. Therefore, the investigator's assessment appears acceptable.*

Patient 30A-10-06 was a 75 year-old male with an underlying non-secreting gastroenteropancreatic liver tumor. The patient's baseline SBP was elevated at 156 mmHg and at the 1 hour assessment the SBP was 163 mmHg; a clinically significant decrease to 108 mmHg was recorded at the 1.5 to 6 hour assessments. No follow-up assessments were reported. The change in blood pressure towards normal was attributed to decreased anxiety by the investigator.

Reviewer's Comment: *Diastolic pressure was found to drop from a baseline of 83mmHg to 74mmHg at the 3-6 hour assessment. Pulse rate on the other had increased from a baseline of 60bpm to 75bpm. Respiration rate appeared stable. There was not 24 hour assessment reported to confirm return to baseline.*

Patient 30A-11-04 was a 51 year-old male with an underlying pancreatic endocrine tumor and liver metastases. The patient's baseline SBP was 110 mmHg; a clinically significant increase in SBP to 160 mmHg was recorded at the 18 to 30 hour assessment. The investigator attributed the change to a surgical procedure.

Reviewer's Comment: *Diastolic pressure was also noted to increase by 20mmHg at the 18-30 hour assessment. All other parameters appeared relatively stable. All laboratory data appeared stable. The investigator's assessment appears acceptable, however, the surgical procedure was not provided and the timing of that procedure was not noted.*

Patient 30B-07-01 was a 39 year-old female with underlying pheochromocytoma. The patient's baseline blood pressure was 95/60 mmHg with a pulse of 92 beats/minute; at the 1.5 to 6 hour assessment the blood pressure had increased to 140/90 mmHg and pulse had decreased to 68 beats/minute. Both changes met the definition of a clinically significant change. At the 18-30 hour assessment, blood pressure remained unchanged, however, pulse had increased to 75 beats/minute. The changes were consistent with pheochromocytoma, which is associated with fluctuations in heart rate and blood pressure.

Reviewer's Comment: *In agreement with the Investigator's assessment.*

Patient 32-01-19 was a 75 year-old male with underlying melanoma. The patient's baseline blood pressure was 138/74 mmHg. Increases in diastolic blood pressure to 100 mmHg were noted at the 30 minute and 1 hour time points; an increase in systolic blood pressure to 190 mmHg was reported at the 1.5 to 6 hour evaluation. The vital signs parameters had returned toward baseline by the 18 to 30 hour assessment. The investigator attributed the changes to underlying hypertension.