

Sponsor's Efficacy Conclusions: The primary efficacy indicator of this study was the patient-based agreement rate of Technetium Tc 99m P829 images with final institutional clinical diagnosis compared with the patient-based agreement rate of indium In 111 pentetreotide images. Indium In 111 pentetreotide results were used as, or contributed to, the final institutional clinical diagnosis. Under these conditions, Technetium Tc 99m P829 is not as effective as indium In 111 pentetreotide in detecting and localizing somatostatin-receptor expressing neuroendocrine tumors. The agreement rates of Technetium Tc 99m P829 with final institutional clinical diagnosis for the three blinded readers ranged from 47.3 to 62.6%. The agreement rates for indium In 111 pentetreotide with final institutional clinical diagnosis for the three blinded readers ranged from 68.8 to 79.1%.

Two explanations for the superior performance of indium In 111 pentetreotide became evident during the study. First, indium In 111 pentetreotide was used as a diagnostic modality for determining the final institutional clinical diagnosis in 92% of evaluable patients. Consequently, blinded reads of indium In 111 pentetreotide images were compared with final institutional clinical diagnosis that used unblinded reads of indium In 111 pentetreotide images in most cases. This circumstance created a bias in favor of the higher agreement rate that was observed for indium In 111 pentetreotide.

A second explanation for the superior performance of indium In 111 pentetreotide concerns problems with imaging the abdomen shortly after administration of Technetium Tc 99m P829. Imaging with Technetium Tc 99m P829 was performed before the non-specific uptake in abdominal structures had time to clear, and the visualization of tumor may have been occluded by background uptake. Imaging with indium In 111 pentetreotide is typically done at least 24 hours post-injection, which allows sufficient time to permit clearance from the abdomen. The sensitivity of indium In 111 pentetreotide images, 76.1%, was also significantly better than that of Technetium Tc 99m P829, 41.3%. Specificity of Technetium

Tc 99m P829 results, 87% agreement for patients who did not have a tumor, was greater than the specificity of indium In 111 pentetreotide results, 82.6%, although the difference was not significant.

These data demonstrate that, for detection and localization of somatostatin-receptor expressing neuroendocrine tumors, Technetium Tc 99m P829 is comparable to indium In 111 pentetreotide in the head/neck, chest and pelvic regions, and in both upper and lower extremities.

Safety: The safety data was not divided and analyzed by dose preparation (heated and unheated). The safety of the heated dose preparation cannot be adequately addressed given the Sponsor's pooled presentation of the data.

Deaths: 0

Withdrawals due to an Adverse Event: 0

Serious Adverse Events: 0

Severe Adverse Events: 0

Extent of Exposure: A total of 135 patients received a single intravenous administration of Tc99m P829. The radioactive dose was ranged from 12.3 to 23.5 mCi and the peptide dose ranged from 7 to 50 µg. The lots used in this study include 9509B01B and D, 9509M01B, 9609B02B-F. A total of 98 patients received the heated dose preparation and 18 received the unheated dose preparation.

Adverse Events: A total of 11 patients experienced 16 adverse events (Table 18). Two patients each experienced diarrhea, abdominal pain and dizziness. One patient experienced diarrhea and abdominal pain which was reported as severe in intensity. This patient, however, did not require treatment. Patient 1-9 experienced GI symptoms which required treatment. Intravenous hydration and morphine was administered to this patient for abdominal pain. The investigator attributed these events to previous similar episodes experienced as a results of a partial bowel obstruction noted 3 weeks prior to enrollment. Two of the 18 adverse events were considered possibly related to the study drug by the investigator (taste perversion and glossitis). No deaths or serious adverse events were reported.

TABLE 18. ADVERSE EVENTS POST TECHNETIUM Tc 99m P829.

Patient	Event (COSTART)	Severity	Min. Post Injection	Duration (Min)	Related To Drug	Treatment
1-5	DIARRHEA	Severe	1070	120	Probably Not	None
	PAIN ABDO	Severe	1070	120	Probably Not	None
1-6	DIARRHEA	Moderate	989	240	Probably Not	None
1-7	ERUCTAT	Mild	554	90	Probably Not	None
1-9	NAUSEA	Moderate	383	600	Probably Not	Yes
	VOMIT					
	PAIN ABDO	Moderate	383	600	Probably Not	Yes
2-5	DIZZINESS	Mild	25	8	Probably Not	None
3-9	VASODILAT	Mild	180	10	Probably Not	None
4-1	DYSPNEA	Mild	149	NR*	Probably Not	None
4-2	PAIN	Severe	23	5	Probably Not	None
	NECK RIGID	Moderate	30	448	Probably Not	None
	PAIN	Moderate	33	85	Probably Not	None
4-16	INJECT SITE REACT	Mild	NR*	NR*	Probably Not	None
4-23	DIZZINESS	Mild	32	90	Probably Not	None
12-3	GLOSSITIS	Mild	NR*	NR*	Possibly	None
	TASTE PERVERS	Mild	25	Ongoing	Possibly	None

Data Source: Sponsor Text Table XLVI, Vol. 139, pg. 0109. * Not Recorded

Comment: The patients that have been bolded in the table above represent those patients who received the [redacted] dose preparation. Patients 3-9 and 4-1 had stable vital sign values reported for all timepoints. Patient 2-5 and 3-9 had relatively stable vital sign values around the time they experienced their adverse event.

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Patient 4-23 had a mild decrease in diastolic pressure, pulse and respiratory rate at the 3-6 hour assessment which returned to baseline by 24 hour.

Laboratory Data:

The following changes in laboratory measurements from baseline values were to be considered clinically significant (with the exception of WBC differential) by the Sponsor:

- i. Baseline within normal range, post-injection value out of normal range and at least a 25% change from baseline.
- ii. Baseline out of normal range (high or low), post-injection value still out of range in the same direction with a 25% further increase or decrease from baseline.
- iii. Baseline missing, post-injection value out of normal range.
- iv. Baseline out of normal range, post-injection value out of range in the opposite direction.
- v. Baseline and post-injection values both within normal range, but post-injection value at least 50% greater than or less than baseline value.

The investigator was to note these changes on the case report form and was to attribute the likely cause of the change in the following manner:

- 1 = Attributable to disease; no follow-up required.
- 2 = Possibly attributable to Technetium Tc 99m P829; FOLLOW-UP REQUIRED,
- 3 = Apparent laboratory error,
- 4 = Unevaluable; includes instances where baseline values not reported.

Hematology: A summary of the mean change from baseline for hematology parameters per timepoint can be found in table 19. No standard deviation was reported. Findings shows statistically significant decreases in mean values for the following parameters: hematocrit (3-6hr.), hemoglobin (3-6 hr.), RBC (1 hr.), neutrophil count (3-6 hr.), eosinophil count (1 & 3-6 hr.) basophil count (1 hr.) and platelet count (1 hr.). Statistically significant increases in mean values over baseline were seen for WBC count 1 & 3-6 hr.) and lymphocyte count (3-6 hr.).

TABLE 19. SUMMARY OF HEMATOLOGY RESULTS. ¹					
TEST		BASELINE N = 113	CHG @ 1 HOUR N = 109	CHG @ 3-6 HOURS N = 111	CHG @ 24 HOUR N = 91
Hematocrit (%)	Mean	39.25	-0.24	-0.55	-0.15
	Sig. Prob.	-	0.164	0.001	0.573
	Range	26.9-51.2	-6.5 to 5.2	-6.0 to 4.6	-5.0 to 3.8
Hemoglobin (g/dL)	Mean	13.15	-0.07	-0.11	-0.02
	Sig. Prob.	-	0.190	0.041	0.896
	Range	9.0-16.3	-1.9 to 1.5	-1.5 to 1.4	-1.4 to 1.1
RBC (x 10 ¹² /L)	Mean	4.32	-0.03	0.00	-0.01
	Sig. Prob.	-	0.033	0.009	0.812
	Range	2.9-6.1	-0.7 to 0.6	-0.6 to 4.8	-0.5 to 0.4
WBC (x 10 ⁹ /L)	Mean	6.85	0.19	0.20	-0.21
	Sig. Prob.	-	0.004	0.035	0.079
	Range	2.2-20.7	-2.4 to 3.3	-2.6 to 3.3	-5.6 to 3.7
Neutrophils (%)	Mean	63.85 (N=112)	0.33	-1.33 (N=110)	-0.43 (N=89)
	Sig. Prob.	-	0.628	0.012	0.145
	Range	20-92	-28.0 to 21.4	-20.0 to 29.5	-28.8 to 29.0
Lymphocytes (%)	Mean	25.67 (N=112)	-0.01	1.32 (N=110)	-0.07 (N=89)
	Sig. Prob.	-	0.998	0.001	0.557
	Range	6.0-70.0	-21.0 to 25.9	-24.1 to 21.9	-29.0 to 18.1
Monocytes (%)	Mean	6.61 (N=112)	0.04	0.22 (N=110)	0.21 (N=89)
	Sig. Prob.	-	0.453	0.334	0.212
	Range	1.0-15.0	-11.5 to 9.0	-8.0 to 6.4	-10.6 to 8.0
Eosinophils (%)	Mean	3.23 (N=112)	-0.29	-0.16 (N=110)	0.22 (N=89)
	Sig. Prob.	-	0.003	0.008	0.663
	Range	0-14	-3.8 to 4.5	-3.2 to 9.7	-3.8 to 6.0
Basophils (%)	Mean	0.63 (N=112)	-0.11	-0.07 (N=110)	0.03 (N=89)
	Sig. Prob.	-	0.028	0.112	0.838
	Range	0-2	-1.5 to 1.4	-1.2 to 1.6	-2.0 to 2.9
Platelets (per mm ³)	Mean	230.99	-1.72	2.42	-0.10 (N=90)
	Sig. Prob.	-	0.048	0.839	0.893
	Range	89-470	-87.0 to 182.0	-80.0 to 136.0	-129.0 to 224.0

¹Significance probability associated with Wilcoxon signed-rank test for differences from baseline.

Data Source: Sponsor Text Table XLVII, Vol. 1.39, pg. 0112, Table S87-S96, Vol. 1.42.

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Shift table analysis for the hematology parameters studied can be found in table 20.

TABLE 20. HEMATOLOGY SHIFT TABLE.			
TEST	PATIENTS WITH SHIFTS		
	@ 1 HOUR N = 109	@ 3-6 HOURS N = 111	@ 24 HOUR N = 91
Hematocrit	6 +, 9 -	2 +, 8 -	5 +, 9 -
Hemoglobin	4 +, 6 -	4 +, 2 -	3 +, 2 -
RBC	3 +, 5 -	4 +, 2 -	2 +, 3 -
WBC	4 +, 4 -	6 +, 4 -	3 +, 6 -
Neutrophils	4 +, 6 -	3 +, 9 - (N=110)	9 +, 4 - (N=89)
Lymphocytes	3 +, 6 -	5 +, 3 - (N=110)	3 +, 12 - (N=89)
Monocytes	1 +, 1 -	1 +, 1 - (N=110)	4 +, 2 - (N=89)
Eosinophils	0 +, 4 -	3 +, 4 - (N=110)	2 +, 2 - (N=89)
Basophils	0 +, 0 -	0 +, 0 - (N=110)	2 +, 0 - (N=89)
Platelets	0 +, 3 -	1 +, 1 -	1 +, 2 - (N=90)

Data Source: Sponsor Text Table XLIX, Vol. 1.39, pg. 0114.

Review of the hematology parameters that met the criteria for a clinically significant change, two patients (1-18 and 14-1) appeared to have unexplained clinically significant drops in platelet counts. Patient 1-18 had a drop in platelet count from baseline of 146 to 24 hour timepoint. The platelet count for this patient at all timepoints are listed below:

baseline:	146.0
1 hr.	234.0
3-6 hr.	282.0
24 hr.	116.0

Patient 14-1 had a significant drop in platelet count at the 1 hour timepoint. This was also accompanied by a drop in hemoglobin, hematocrit and RBC values at the same time point. The platelet count for this patient is listed below: The investigator attributed this drop in platelet count as lab error.

baseline:	170.0
1 hr.	83.0
3-6 hr.	287.0
24 hr.	199.0

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Of those patients with abnormal hemoglobin levels, two patients (4-10 and 14-1) appeared to have unexplained clinically significant drops in hemoglobin levels.

Table 21. Significant Changes in Hemoglobin Values (G/DL)

Timepoint	Patient 4-10	Patient 14-1
Baseline	13.3	9.1
1 hr.	13.2	7.9
3-6 hr.	12.5	9.3
24 hr.	11.9	9.35

Data Source: Table S83, vol. 1.42.

Of those with abnormal eosinophil counts, four patients appeared to have significant rises in values compared to baseline. The eosinophil levels per timepoint and patient can be found below. No symptoms were reported by these patients and all values except for patient 7-12 had values that remained within the normal range. The clinical meaning of this finding is not known. The investigator did not comment on these values.

Table 22. Significant Changes in Eosinophil Counts (%) per Patient

Timepoint	Patient 1-6	Patient 3-2	Patient 4-5	Patient 7-12
Baseline	2	0	5	3
1 hr.	4	2	6	5
3-6 hr.	7	7.2	7	12.7
24 hr.	8	5.5	10	1.8

Data Source: Table S84, vol. 1.42.

No abnormal hematologic abnormality was considered related to the test drug as per the investigator.

Chemistry: Mean changes from baseline for all patients at the various timepoints are listed in Table 23. Statistically significant drops in values were seen for the following parameters: ALT (3-6 hr.), Alk. Phos. (1 hr.), total protein (3-6 hr.) and BUN (3-6 hr.). A statistically significant increase in the mean creatinine value was seen at the 3-6 hr. timepoint.

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TABLE 23. SUMMARY OF CLINICAL CHEMISTRY RESULTS. ¹					
TEST		BASELINE	CHG @	CHG @	CHG @
		N = 111	1 HOUR N = 108	3 - 6 HOUR N = 107	24 HOUR N = 90
AST (SGOT) (U/L)	Mean	24.18	0.19	-0.28	-0.01
	Sig. Prob.	-	0.824	0.344	0.551
	Range	8.0-154.0	-39.0 to 41.0	-37.0 to 45.0	-53.0 to 52.0
ALT (SGPT) (U/L)	Mean	25.35	-0.10	-0.33	0.78
	Sig. Prob.	-	0.349	0.006	0.238
	Range	6.0-133.0	-8.0 to 12.0	-11.0 to 31.0	-18.0 to 43.0
Alka. Phos. (U/L)	Mean	105.56	-0.79	-0.92	0.71
	Sig. Prob.	-	0.029	0.085	0.892
	Range	22.0-654.0	-39.0 to 67.0	-41.0 to 46.0	-47.0 to 100.0
LDH (U/L)	Mean	180.05	4.69	-6.90	-3.72
	Sig. Prob.	-	0.676	0.184	0.196
	Range	83.0-900.0	-461 to 572	-498 to 148	-537 to 276
Total Bili. (mg/dL)	Mean	0.64	0.02 (N=106)	0.02 (N=108)	0.04
	Sig. Prob.	-	0.394	0.327	0.125
	Range	.20-1.83	-0.24 to 0.90	-0.30 to 0.90	-0.40 to 0.90
Total Protein (g/dL)	Mean	7.08 (N=112)	-0.06 (N=109)	-0.10 (N=109)	-0.09 (N=91)
	Sig. Prob.	-	0.057	0.016	0.081
	Range	5.50-9.10	-1.60 to 1.90	-1.10 to 1.20	-1.50 to 0.90
BUN (mg/dL)	Mean	15.83 (N=112)	-0.21 (N=109)	-0.39 (N=109)	0.18 (N=91)
	Sig. Prob.	-	0.112	0.012	0.605
	Range	5.0 to 51.0	-6.0 to 5.0	-7.0 to 6.0	-6.0 to 7.0
Creatinine (mg/dL)	Mean	0.99 (N=112)	-0.02 (N=109)	0.02 (N=109)	0.01 (N=91)
	Sig. Prob.	-	0.126	0.030	0.405
	Range	0.46-2.90	-0.40 to 0.44	-.050 to 0.48	-0.40 to 0.25

¹Significance probability associated with Wilcoxon signed-rank test for non-zero change.

Data Source: sponsor Text Table XLVIII, Vol. 1.39, pg. 0113, Table S97-S104, Vol. 1.42.

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Shift table analysis for the chemistry parameters studied can be found in table 24.

TEST	PATIENTS WITH SHIFTS		
	@ 1 HOUR N = 108	@ 3-6 HOURS N = 107	@ 24 HOUR N = 90
AST (SGOT)	1 +, 0 -	1 +, 0 -	1 +, 0 -
ALT (SGPT)	0 +, 0 -	0 +, 0 -	2 +, 0 -
Alkaline Phosphatase	0 +, 2 -	1 +, 2 -	0 +, 2 -
LDH	3 +, 2 -	2 +, 2 -	6 +, 2 -
Total Bilirubin	0 +, 0 - (N=106)	2 +, 0 - (N=108)	2 +, 0 -
Total Protein	1 +, 2 - (N=109)	1 +, 2 - (N=109)	0 +, 4 - (N=91)
BUN	1 +, 1 - (N=109)	1 +, 1 - (N=109)	1 +, 4 - (N=91)
Creatinine	4 +, 4 - (N=109)	7 +, 3 - (N=109)	4 +, 2 - (N=91)

Data Source: sponsor Text Table L, Vol. 1.39, pg. 0115.

Of the LDH values reported as abnormal by the Sponsor (Table S85, Vol. 1.42, pg. 039), the following were considered significant changes as per this reviewer:

Table 25. Significant Changes in LDH (U/L) Values Per Patient

Timepoint	Patient 1-7	Patient 1-18	Patient 5-9	Patient 6-2	Patient 10-12	Patient 11-10
Baseline	224	208	160	136	156	199
1 hr.	173	210	146	218	161	677
3-6 hr.	194	168	152	212	253	150
24 hr.	353	343	436	370	--	137

Data Source: Table S85, vol. 1.42.

The investigator reported the abnormal values for patient 1-7 and 11-10 as attributable to lab error, value for patients 1-18 and 10-12 as attributable to disease, values for patient 5-9 as unevaluable and values for patient 6-2 as possibly related to the study drug. Patient 1-7 had an associated elevation seen in alkaline phosphatase as well.

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Of the patients with abnormally elevated AST values, three patients had values thought to be considered as a significant changes from baseline:

Table 26. Significant Changes in AST Values (U/L) per Patient

Timepoint	Patient 1-9	Patient 11-10	Patient 12-2
Baseline	18	22	28
1 hr.	16	63	37
3-6 hr.	17	19	73
24 hr.	70	18	28

Data Source: Table S85, vol. 1.42.

Patient 1-9 had an associated elevation in ALT for the same timepoint. Patient 12-2 had other liver function tests which were elevated at baseline as well as for the post injection timepoints. The Sponsor attributes the changes occurring in patient 12-2 as possibly related to study drug. Patient 11-10 changes were considered as lab error and patient 1-9 changes were considered disease related.

Comment: Scatter plot data was not useful because the Sponsor applied a cutoff of $\pm 70\%$ of baseline as identifying an outlier. This cut off was too broad and does not provide adequate analysis of the data.

Vital Sign Data: Clinically significant changes in vital sign parameters were defined by the Sponsor as those meeting the following cut off points:

- systolic blood pressure ± 35 mm Hg
- diastolic blood pressure ± 25 mm Hg
- pulse ± 20 beats/minute
- respiratory rate ± 10 breaths/minute

Comment: These cutoff points are liberal. Generally a cut off point of ± 20 mmHg and $\pm 10-15$ mmHg for systolic and diastolic pressures respectively is recommended.

Brief review of the line listings (Vol. 1.42, Table 16) applying a cutoff point of a change greater than ± 20 mmHg for systolic pressure and greater than ± 10 mmHg for diastolic pressure, the following was identified:

Twenty-two patients had abnormal diastolic blood pressure values. Of the 22, 12 were increases and 10 were decreases. Of the 12 patients experiencing an increase, 3 patients had 2 or more consecutive timepoints where the pressure was elevated. Of the 10 patients with decreases, 3 patients had 2 or more consecutive timepoints where the pressure decreased from baseline.

Fourteen patients had abnormal systolic blood pressure values. Of the 14, 7 patients had increased systolic values and 7 patients had decreased systolic values. Of those experiencing increases, 1 patient had 2 or more consecutive timepoints where the systolic pressure was elevated. Of the 7 patients experiencing a decrease, 3 patients had 2 or more consecutive timepoints where the pressure was decreased.

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Three patient had either corresponding changes in systolic and diastolic blood pressure or accompanying changes in pulse and respiratory rate. These three patients (1-1, 1-2 and 1-4) all received the unheated market formulation.

The Sponsor presented the patient incidence of clinically significant changes in vital signs classified according to COSTART term in the table 27 below.

TABLE 27. INCIDENCE OF CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS, N = 117.

COSTART	NUMBER OF PATIENTS	%
Bradycardia	4	3.4
Hypertension	4	3.4
Hyperventilation	3	2.6
Hypotension	3	2.6
Tachychardia	2	1.7
Hypoventilation	2	1.7

Data Source: Sponsor Text Table LVI, Vol. 1.39, 093.

The only clinically significant change in vital signs considered by the investigator to be possibly attributable to Technetium Tc 99m P829 was the hypertension in Patient 6-4. Blood pressure in Patient 6-4 increased from 137/82 mmHg at baseline to 187/95 mmHg at 3 - 6 hours, and returned to 130/74 mmHg at 24 hours.

Comment: Patient 6-4 had an increase in systolic, diastolic blood pressure as well as pulse and respiratory rate at the 3-6 hr. timepoint. Blood pressure returned toward baseline at the 24 hr. timepoint but pulse and respiratory rate remained elevated. The Sponsor did not identify if the patient experienced symptoms during this period. No adverse events were reported for this patient.

Sponsor's Safety Conclusions:

Technetium Tc 99m P829 was well tolerated by patients. Eleven of 117 patients (9.4%) who received the study drug reported 16 adverse events. There were no overall mean changes in hematology or clinical chemistry results to suggest changes caused by Technetium Tc 99m P829. Statistically significant changes were noted in some parameters but they were either in a favorable direction or were clinically insignificant. Additionally, there were no statistically significant shifts noted for hematology or chemistry values in this study.

There were fourteen clinically significant changes, according to the sponsor's criteria, in individual hematology values noted by the investigators. None of these were considered possibly attributable to Technetium Tc 99m P829. Seven were noted to be disease related and seven were attributed to laboratory error.

Technetium Tc 99m P829 was considered the possible cause in only seven of the 79 investigator-noted clinically significant changes in clinical chemistry results. Six of the seven values had returned to baseline at follow-up; there was no follow-up for one patient.

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There were eighteen clinically significant changes in vital signs reported; the site investigator noted that one of the changes was possibly related to the Technetium Tc 99m P829 injection. In general Technetium Tc99m P829 was well tolerated and safe.

Reviewer's Discussion:

Efficacy/Design: The primary endpoint of the patient based rate of agreement is not acceptable to support efficacy for a phase 3 trial. Rate of agreement does not provide information regarding the false positive and false negative results experienced when this agent is used. This information severely impact on patient management and must be assessed for any diagnostic test. The "patient-based" agreement does not accurately allow for concordance between the modality and truth. A site by site comparison offers a better analysis of the performance of the drug. Overall, a site by site analysis including agreement, sensitivity and specificity calculations, using biopsy as the standard of truth, should have been performed.

In review of the region analysis, Tc99m P829 performed comparably to In-111 pentetreotide for all regions except the chest and abdomen. For the individual blinded readers, agreement rated for the chest and abdomen were 9-11% higher and 15-33% higher for In-111 pentetreotide respectively. These differences were found to be statistically significant. The reason for the discrepancy between the two modalities in these two regions is not fully known. The Sponsor anticipates that there was bias introduced by the fact that the In-111 pentetreotide images were also used to enroll patients. Usually the comparator should not also be the standard of truth. A standard should be as close to 100% when diagnosing truth, therefore, In-111 pentetreotide with its sensitivity and specificity for diagnosing somatostatin receptor expressing tumors, room for bias is possible. However, both Tc99m P829 and In-111 pentetreotide are both somatostatin analogues which are purported to bind to somatostatin receptors, it is not unrealistic to anticipate close agreement between the two modalities. The differences seen in the abdomen could be related to the mode of excretion and the timing of the imaging. As seen with In-111 pentetreotide, delayed imaging is recommended to allow for clearing of the non-specific uptake normally seen in the abdomen. Given this and the fact that the major route of elimination of Tc99m P829 has yet to be identified, this issue of non-specific binding and appropriate imaging time for abdominal imaging has not adequately been addressed by the Sponsor. The differences seen in the chest are not fully understood and would require further study to anticipate if this difference was solely due to the potential bias introduced by having In-111 as the standard and enrolling criteria.

Analysis by primary lung tumor revealed comparability between the two modalities in the 14 patients studied.

This study utilized both the heated and unheated dose preparation of the drug. No efficacy comparison between the dose preps was made.

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Safety:

A limited safety review was performed for several reasons. The criteria used to distinguish a clinically significant change in vital sign parameters were too liberal. Generally, a cutoff of ± 20 mmHg for systolic and ± 10 mmHG for diastolic pressures are usually applied. Also, the cutoff the Sponsor applied for the scatter plot analysis was not adequate.

With regards to laboratory data, analysis of the mean change from baseline is not the best way to identify trends in the data. Scatter plots offer a better look at trends, however, the cutoff point to identify an outlier, was far too liberal. The scatter plots thus were not too useful.

A brief review of systolic and diastolic pressures applying the cutoff points stated above obviously revealed a larger number of patients who experienced changes in blood pressure than reported in the Sponsor's review. Further analysis by the Sponsor should be done to confirm these findings and provide rationale as to their clinical meaning.

This study utilized both the heated and unheated dose preparation of the drug. No safety comparison between the dose preps was made.

Reviewer's Conclusion:

The design of this study severely limits the potential efficacy claims that this trial could support. The Sponsor showed that Tc99m P829 was similar to In 111 pentetreotide in identifying somatostatin receptor expressing tumors in all regions of the body except the abdomen and possibly the chest. Further study as to the adequate dose and image timing for study of the abdomen with this drug is needed.

Statements regarding safety are limited. Given the Sponsor's analysis there does not appear to be significant safety concerns.

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Phase 3
Study P829-30B

11.8 Study P829-30B

Phase 3, P829-30B (Volumes 1.50-1.60) Additional Information submitted after filing with letter dates 7/9/98 and 7/28/98.

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

Formulation: Market Formulation

Population: Patients with Neuroendocrine Tumors

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

Objectives:

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

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

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

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

Table 1. Time Table of Events

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

Results:

Protocol Violations: Six patients were found to have violations in one or more of the inclusion/exclusion criteria. Patients 12-1, 12-4, and 12-6 were enrolled without a documented clinical history of Neuroendocrine tumors and did not have an indium In-111 Pentetreotide study completed or scheduled. Patients 1-13, 1-15 and 1-22 had changes in their Octreotide therapy regimen before on the day of study participation or after In-111 Pentetreotide imaging. Patient 1-15 did not have an indium In-111 Pentetreotide study. The Sponsor considered patients 1-13, 1-15 and 1-22 as protocol deviators rather than violators.

Protocol Deviations: As per the Sponsor, there were 7 patients which had In-111 Pentetreotide imaging at times other than specified by the protocol. These patients were identified as deviating from the protocol. This number could not be verified as the sponsor did not adequately reference the raw data for confirmation.

Disposition:

A total of 135 patients were enrolled at 6 United States sites and at 4 European sites. Seven patients did not complete either Tc99m P829 or In-111 Pentetreotide imaging and were excluded from the efficacy analysis. The disposition by study site can be found in Table 2.

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Table 2. Disposition by Study Site

Study Site	Number of Patients Enrolled
1	40
2	13
3	2
4	8
5	9
6	6
7	7
9	24
11	17
12	9
TOTAL	135

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

Demographics: Summary statistics for age weight, height, gender and race are provided for all patients and for the evaluable patient population in tables 3-4. Mean age of the efficacy evaluable population was 54.7 years with a range of 19.9 to 80.8 years. Approximately 42% of the evaluable population were female and 58% were male. The majority (85%) of the population was Caucasian. Since there was only a difference of 7 patients between the intent-to-treat (ITT) population and efficacy evaluable population, demographic information for the efficacy evaluable population was representative of that for the ITT population.

		N	MIN.	MAX.	MEAN	STD. DEV.
Age (yr)	All Patients	135	19.9	80.8	54.7	13.8
	Evaluable Patients	128	19.9	80.8	54.9	13.8
Height (cm)	All Patients	131	144.8	193.0	169.8	10.1
	Evaluable Patients	124	144.8	193.0	170.0	10.1
Weight (kg)	All Patients	133	44.1	150.0	73.7	16.6
	Evaluable Patients	126	44.1	150.0	73.7	16.4

Data Source: Sponsor Text Table VIII., Vol. 1.50, pg. 058.

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		All Patients		Evaluable Patients	
		N	%	N	%
GENDER	Female	58	43.0	54	42.2
	Male	77	57.0	74	57.8
	TOTAL	135	100	128	100
RACE	Black	10	7.4	7	5.5
	White	113	83.7	109	85.2
	Other	12	8.9	12	9.4
	TOTAL	135		128	

Data Source: Sponsor Text Table IX., Vol. 1.50, pg. 059.

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

TYPE	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
Carcinoid	41	30.4	41	32.0
Small Cell Lung	11	8.1	11	8.6
Gastrinoma	7	5.2	7	5.5
Medullary Thyroid Carcinoma	7	5.2	7	5.5
Non-Specific Neuroendocrine	7	5.2	7	5.5
Endocrine Pancreatic	5	3.7	5	3.9
Paraganglioma	5	3.7	2	1.6
Melanoma	4	3.0	4	3.1
Insulinoma	2	1.5	2	1.6
Pheochromocytoma	2	1.5	2	1.6
Parathyroid	1	0.7	1	0.8
Non- Small Cell Lung Cancer	1	0.7	1	0.8
Growth-Hormone Producing Pituitary	1	0.7	1	0.8
Other	10	7.4	10	7.8
ANY TYPE ¹				

¹ Numbers represent patients confirmed with these tumors. Percentages are relative to all patients (135) or to total evaluable patients (128).

Data Source: Sponsor Text Table X., Vol. 1.50, pg. 060.

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

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Table 6. Tumor Type Localized in the Lungs

TUMOR TYPE	N
Small Cell	9
Large Cell	1
Non-small Cell	1
Thyroid Cancer (metastatic)	2
Carcinoid	1
Neuroendocrine	1
Paranglioma	1
Spindle Cell	1

Data Source: Table 3, Vol. 1.55, Appendix 16.2, pg. 017.

A table showing the location of tumor presentation can be found below (table 7). The majority of lesions presented in the gastrointestinal tract. Ten percent of the efficacy evaluable population had tumors presenting in the lungs (n=13).

LOCATION	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
Gastrointestinal	23	17.0	23	18.0
Lung	13	9.6	13	10.2
Pancreas	11	8.1	11	8.6
Thyroid	6	4.4	6	4.7
Adrenal	3	2.2	3	2.3
Liver	2	1.5	2	1.6
Pituitary	2	1.5	2	1.6
Abdomen	1	0.7	1	0.8
Unknown ¹	4	3.0	4	3.1
Not Specified ²	2	1.5	2	1.6
Other ³	28	19.3	25	18.3

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

² Not specified represents tumors that were confirmed but no location was indicated.

³ Other includes tumors whose locations were indicated on the CRF but were not one of the categories listed in the above table.

⁴ Numbers represent confirmed tumors. Percentage is relative to all patients (135) or to total evaluable patients (128).

Data Source: Sponsor Text Table XI, Vol. 1.50, pg. 061.

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The modality used to diagnose patients at the time of enrollment can be found in table 8. Computed tomography was the most common modality used (71%) followed biopsy which was performed in 48% of the efficacy evaluable population. Of the 13 patients presenting with tumor in the lung, diagnostic modalities used to confirm disease include CT (10 patients), X-ray (6 patients), In-111pentetreotide (5 patients), biopsy (5 patients), MRI (2 patients), surgery (6 patients), hormone levels (2 patients) and clinical chemistry levels (1 patient).

TABLE 8. PATIENT DISTRIBUTION OF MODALITIES EMPLOYED IN INITIAL DIAGNOSIS OF PRESENTING TUMORS ON A BY-PATIENT BASIS.				
MODALITY	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
CT	92	68.1	91	71.1
Biopsy	62	45.9	62	48.4
Hormone Levels	62	45.9	61	47.7
Surgery	60	44.4	57	44.5
In 111 Pentetreotide	54	40.0	52	40.6
Ultrasound	29	21.5	28	21.9
Clinical Chemistry	22	16.3	22	17.2
MRI	21	15.6	19	14.8
X-ray	17	12.6	17	13.3
PET	4	3.0	4	3.1
Other	25	18.5	19	14.8

Data Source: Text Table XII, Vol. 1.50, pg. 061.

A listing of the number of patients receiving somatostatin analog therapy during this study can be found in table 9. One of the 13 patients presenting with tumor in the lung were on somatostatin analog therapy (patient 2-6, octreotide therapy, 1,200 mcg).

TABLE 9. DISTRIBUTION OF SANDOSTATIN® OR OTHER SOMATOSTATIN ANALOG USAGE.				
MEDICATION	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
Sandostatin® (octreotide)	11	8.1	11	8.6
Somatostatin	2	1.5	2	1.6
Somatuline	2	1.5	2	1.6
NONE	120	88.9	113	88.3
TOTAL	135		128	

Data Source: Sponsor Text Table XIII., Vol. 1.50, pg. 062.

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

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

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

Drugs for the treatment of peptic ulcers, taken by 32 evaluable patients (25%), and thyroid preparations, taken by 21 evaluable patients (16.4%), were the most commonly used classes of concomitant medications, followed by beta-blocking agents. Ninety-two percent of the evaluable patients had taken at least one medication within 24 hours of the study (table 11).

MEDICATION	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
Treatment of Peptic Ulcers	33	24.4	32	25.0
Thyroid Preparations	22	16.3	21	16.4
Beta-Blocking Agents	14	10.4	13	10.2
Agents Acting on Renin-Angiotensin System	14	10.4	14	10.9
Opioids	12	8.9	12	9.4
Antidepressants	12	8.9	12	9.4
Other	96	71.1	93	72.7
Any Medication (one or more medications)	110	91.5	107	83.6
TOTAL	135		128	

Data Source: Sponsor Text Table XV., Vol. 1.39, pg. 064.

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

TABLE 12. DISTRIBUTION OF INTERVAL BETWEEN TECHNETIUM Tc 99m P829 AND INDIUM In 111 PENTETREOTIDE PROCEDURE.				
TIMING OF INDIUM In 111 PENTETREOTIDE	ALL PATIENTS		EVALUABLE PATIENTS	
	N	%	N	%
60 d. to 7 d. prior	41	30.4	41	32.0
7d. prior to < 1 d. post	5	3.7	5	3.9
1 d. post to 14 d. post	80	59.3	80	62.5
> 14 d. post	2	1.5	2	1.6
No study performed	7	5.2	0	0
TOTAL	135		128	

Data Source: Sponsor Text Table XVII., Vol. 150, pg. 066.

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

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TABLE 13. PATIENTS WHOSE IMAGES WERE NOT EVALUATED FOR EFFICACY BY ONE OR MORE BLINDED READERS.		
	PATIENT	READER NUMBER(S)
Indium In 111 pentetreotide images considered to be of nondiagnostic quality.	1-27	1
	2-1	1
	2-3	3
	2.8	1 and 3
	2-11	1 and 3
	4-3	1 and 3
	4-5	3
	4-7	1
	4-8	3
	11-5	1
Technetium Tc 99m P829 images considered to be of nondiagnostic quality.	4-8	1
No definitive In-111 pentetreotide diagnosis for any of the regions considered positive by final institutional clinical diagnosis	1-24	2
	2-2	2
Insufficient number of regions with definitive final institutional clinical diagnosis and indium In-111 pentetreotide diagnosis to support negative agreement	2-8	2
	6-3	2
Insufficient number of regions with definitive Technetium Tc-99m P829 diagnosis to support negative agreement	2-8	1,2 and 3
	5-7	2 and 3
	7-6	1 and 2

Data Sponsor: Sponsor Text Table VI., Vol. 1.50, page 056.

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

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

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

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

REGION	SIDE	DIAGNOSIS			TOTAL PTS WITH DX
		NO TUMOR NUMBER (%)	TUMOR NUMBER (%)	NOT DONE	
Head/Neck	L	96 (80.7)	23 (19.3)	9	119
	R	99 (83.2)	20 (16.8)	9	119
Chest	L	93 (73.8)	33 (26.2)	2	126
	R	84 (67.2)	41 (32.8)	3	125
Abdomen	L	82 (64.1)	46 (35.9)	0	128
	R	66 (51.6)	62 (48.4)	0	128
Pelvis	L	114 (90.5)	12 (9.5)	2	126
	R	110 (87.3)	16 (12.7)	2	126
Upper Extremity	L	71 (93.4)	5 (6.6)	52	76
	R	71 (93.4)	5 (6.6)	52	76
Lower Extremity	L	65 (91.5)	6 (8.5)	57	71
	R	68 (95.8)	3 (4.2)	57	71
All Patients		23 (18.0)	105 (82.0)	0	128

Data Sponsor: Sponsor Text Table XIX., Vol. 1.50, page 068.

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

TUMOR TYPE	N	%
Carcinoid	43	33.6
Gastrinoma	10	7.8
Medullary Thyroid Carcinoma	7	5.5
Neuroendocrine	7	5.5
Pheochromocytoma	5	3.9
Endocrine Pancreatic Tumor	4	3.1
Insulinoma	4	3.1
Melanoma	4	3.1
Pituitary	4	3.1
Non-small Cell Lung cancer	3	2.3
Small Cell Lung Cancer	3	2.3
Prolactinoma	3	2.3
Adrenal	2	1.6
Islet Cell	2	1.6
Paraganglioma	2	1.6
Thyroid	2	1.6
Other	8	6.3
ANY TYPE	105	82.0

Data Sponsor: Sponsor Text Table XX., Vol. 1.50, page 069.

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Indium In 111 pentetreotide was used in determining the final institutional clinical diagnosis for 122 of the 128 evaluable patients (95.3%). Eighty-two patients (64.1%) had a CT scan. Biopsy was used for approximately 47% of evaluable patients.

Patient-based Analysis: The patient-based rates of agreement and sensitivity calculations per blinded reader reveal that In-111 pentetreotide consistently outperformed (statistical significance seen) Tc99m P829. For specificity calculations, no statistical difference was seen between the two modalities when compared to the final institutional diagnosis. (See Volume 1.50, pages 71-74 for actual results)

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

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

Anatomic Region	N	Agreement Range (%)	Statistical Significance*
Head/Neck			
Tc99m P829	98-114	79-83	No
In-111 pentetreotide	97-108	82-83	
Chest			
Tc99m P829	116-122	77-78	No
In-111 pentetreotide	116-120	82-87	
Abdomen			
Tc99m P829	119-125	54-59	Yes
In-111 pentetreotide	119-124	72-83	
Pelvis			
Tc99m P829	114-123	81-84	No
In-111 pentetreotide	116-121	84-89	
Upper Extremities			
Tc99m P829	40-63	84-91	No
In-111 pentetreotide	37-57	93-98	
Lower Extremities			
Tc99m P829	44-60	90-96	No
In-111 pentetreotide	45-57	97-98	

Data Source: Text Tables XXV, XXVI, XXVII-XXX, Vol. 1.50. *McNemar's χ^2 statistic

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