Reviewer's Comment: *The patient's blood pressure waxed and waned over the 5 minute and 30 minute assessment but increased steadily for both the 60 minute and 2-4 hour assessment. As the Sponsor stated, the values began to return toward baseline at the 18-30 hour assessment. No symptoms were reported. This change in blood pressure was not flagged as clinically significant by the Sponsor in the study data listing (Volume 81, Listing 15).*

The Sponsor noted that the vital sign changes seen in the Phase 1 studies were found to be small and not clinically relevant. Clinically significant changes were noted in these studies with the most changes seen in pulse rate. The Sponsor did not attribute any of the clinically significant findings attributable to the study drug.

Comment: *The Sponsor did not provide summary statistics for the pooled vital sign data for the Phase 1 studies. It is not clear why vital sign parameters were not summarized for all studies (Phase 1 through Phase 3). The Sponsor also gathered temperature data for several of the studies but failed to summarize this data.*

Clinical Laboratory Data:

Clinical laboratories were collected in 11 of 14 clinical studies (all Phase 3 and 1 studies and 2 of the 5 Phase 2 studies). The clinical laboratories monitored per study can be found in Table 4 above. For purposes of the integrated summary of safety, the Sponsor has reported pooled data for the Phase 2 and 3 studies. The data from the Phase 1 studies were reported separately. The data presented by the Sponsor includes the following individual laboratory parameters:

Hematology	Serum Chemistry
Hematocrit	Alkaline Phosphatase
Hemoglobin	Aspartate Transaminase
Red Blood Cell Count	Alanine Transaminase
White Blood Cell Count	Lactate Dehydrogenase
Neutrophils	Total Protein
Basophils	Blood Urea Nitrogen
Eosinophils	Creatinine
Lymphocytes	
Monocytes	
Platelet Count	

Comment: *Multiple safety parameters were studied beyond those listed above, however, since the above parameters were what was assessed in the pivotal studies, the Sponsor only reviewed this data for the Integrated Summary of Safety. Other safety data collected was not pooled and analyzed. This data includes several serum chemistry parameters, urinalysis and temperature data.*

All studies included in the laboratory analyses did not contribute more than once to the following collapsed time points: 1 hour, 2-6 hours and 18-30 hours post-injection. For the pivotal Phase 3 studies, a 1 hour post-injection laboratory evaluation was not performed. Laboratory values that fell into predefined cut point categories and that represented at least a 25% change from the pre-injection value were defined as clinically significant changes. The 25% increase or decrease from baseline was added to the cut point definitions because many of the patients enrolled in these studies had abnormal or borderline abnormal values at the pre-injection assessment. The cut points used for determining clinically significant values per parameter can be found in Appendix F.

Serum Chemistries: The mean changes from pre-injection values to post-injection values per time point for pooled Phase 2 and 3 data can be found in Table 11.

Table 11. Summary of Mean Changes from Pre-Injection to Each Post-Injection Evaluation for Clinical Chemistry Parameters (Population: All Phase 2 & 3 Studies[1])

Clinical Chemistry Parameter	Pre-injection (N = 737)	Change to Post-Injection Evaluation: 1 hr. (N = 224)	2 – 6 hr. (N = 552)	18 – 30 hr. (N = 674)
Alkaline phosphatase (U/L)	100.8 (6-1383)	-2.27	-1.78	-0.04
AST (SGOT) (U/L)	25.9 (6-262)	-0.68	-1.38	-1.19
ALT (SGPT) (U/L)	25.7 (0-426)	-0.54	-0.41	0.22
LDH (U/L)	208.6 (65-2187)	-5.51	-8.33	-16.63
Total Protein (mg/dL)	7.1 (4-10)	-0.13	-0.09	-0.09
Total Bilirubin (mg/dL)	0.6 (0.01-4.80)	0.00	0.01	0.03
BUN (mg/dL)	15.9 (3-108)	-0.26	-0.46	0.12
Creatinine (mg/dL)	1.0 (0.10-5.40)	-0.02	0.00	0.02

1 Ns are for BUN; for other laboratory values see Table 8.3.0 in Section 17
Source: Section 17, Table 8.3.0.

Data Source: Sponsor ISS, Vol. 1.84, Table 15

Mean changes in AST, ALT, and alkaline phosphatase were approximately 2 U/L or less at all post-injection time points; most mean changes in these parameters were usually decreases indicating normalization. Mean changes in LDH were more variable; again, the mean changes were decreases indicating normalization in this variable. Mean total protein decreased by ≤ 0.13 mg/dL and mean total bilirubin increased by ≤ 0.05 mg/dL at all evaluations. Mean changes in BUN and creatinine were variable; the maximum mean increases observed of 0.12 and 0.02 mg/dL for BUN and creatinine, respectively. The Sponsor did not find these changes to be clinically meaningful.

Occurrence of clinically significant changes for clinical chemistry parameters can be found in Table 12.

Table 12. Summary of Clinically Significant Changes from Pre-Injection to Post-Injection Evaluation for Clinical Chemistry Parameters

Laboratory Parameter	Number (%) of Patients	
	Pivotal Phase 3 Studies[1]	All Phase 2 & 3 Studies
Alkaline phosphatase (U/L)	0/249 (0%)	1/661 (<1%)
AST (SGOT) (U/L)	1/261 (<1%)	3/670 (<1%)
ALT (SGPT) (U/L)	3/261 (1%)	5/670 (<1%)
LDH (U/L)	1/245 (<1%)	2/652 (<1%)
Total Protein (mg/dL)	0/261 (0%)	1/630 (<1%)
Total Bilirubin (mg/dL)	2/261 (<1%)	6/667 (<1%)
BUN (mg/dL)	1/261 (<1%)	4/674 (<1%)
Creatinine (mg/dL)	0/261 (0%)	0/673 (0%)

1 Includes Studies 829-34A & B, patients with suspicion of cancer in the lung
Source: Section 17, Table 8.7.0.

Data Source: Sponsor ISS, Vol. 1.84, Table 18

The majority of clinically significant changes occurring in the pooled Phase 2 and 3 studies were reported in less than 1%. As seen above 1% of the patients reported clinically significant changes in ALT for the Phase 3 pivotal trials.

Hematology:

The mean changes from baseline for post-injection timepoints for all Phase 2 and 3 studies for all hematology parameters are presented in Table 13.

Table 13. Summary of Mean Changes from Pre-Injection to Each Post-Injection Evaluation for Hematology Parameters (Population: All Phase 2 & 3 Studies)

Hematology Parameter	Pre-injection (N = 721)	Change to Post-Injection Evaluation:		
		1 hr. (N = 226)	2 – 6 hr. (N = 536)	18 – 30 hr. (N = 636)
Hematocrit (%)	39.8	-0.42	-0.42	-0.15
(range)	(18.9-55.9)			
Hemoglobin (mg/dL)	13.2	-0.14	-0.10	-0.06
(range)	(6.4-17.8)			
RBC ($x10^6/mm^3$)	4.3	-0.04	-0.03	-0.02
(range)	(2.1-6.3)			
WBC ($x10^3/mm^3$)	7.5	0.14	0.17	-0.12
(range)	(1.1-108.2)			
Platelets ($x10^3/mm^3$)[2]	243.3	-2.44	-0.71	2.50
(range)	(26-658)			

1 Ns are for hematocrit and hemoglobin, for other laboratory values see Table 8.3.0 in Section 17
Source: Section 17, Table 8.3.0.

Data Source: Sponsor ISS, Vol. 1.84, Table 17 modified

Mean changes from pre-injection to each post-injection evaluation for all hematology parameters were small and not clinically meaningful. Slight decreases in mean hematocrit, hemoglobin, and RBC count were observed although the mean changes were not clinically significant. Mean WBC count increased and mean platelet count decreased slightly at most time points; again the changes were not clinically meaningful. Occurrence of clinically significant changes for hematology parameters for the pooled Phase 2 and 3 data can be found in Table 14.

Table 14. Summary of Clinically Significant Changes from Pre-Injection to Post-Injection Evaluation for Hematology Parameters

Laboratory Parameter	Number (%) of Patients	
	Pivotal Phase 3 Studies[1]	All Phase 2 & 3 Studies
Hematocrit (%)	0/244 (0%)	2/636 (<1%)
Hemoglobin (mg/dL)	0/244 (0%)	2/635 (<1%)
RBC (x106/mm3)	0/244 (0%)	2/635 (<1%)
WBC (x103/mm3)	1/244 (<1%)	8/607 (1%)
Neutrophils (%)	0/244 (0%)	2/611 (<1%)
Basophils (%)	0/244 (0%)	3/617 (<1%)
Eosinophils (%)	1/244 (<1%)	7/618 (1%)
Monocytes (%)	0/244 (0%)	1/619 (<1%)
Platelets (x103/mm3)	0/234 (0%)	1/589 (<1%)

1 Includes Studies 829-34A & B, patients with suspicion of cancer in the lung
Source: Section 17, Table 8.7.0.

Data Source: Sponsor ISS, Vol. 1.84, Table 19

Clinically significant changes were identified in 1% or less of the patients. In the pooled phase 2 and 3 studies clinically significant changes occurring in 1% of the patients was seen with white blood cell count and eosinophil count. In the case of WBC count, 2 of the 8 changes were noted to be increases and the remaining 6 were found to be decreases. Elevation in eosinophil counts were reported in seven patients (1%); four were transient elevations reported at the 1 hour or 2 to 4 hour assessment with return to baseline at the 18 to 30 hour assessment. No allergic-like adverse events were reported in any of these patients.

Comment: Outliers in laboratory data were not initially provided by the Sponsor. Upon request, the Sponsor provided scatter plots for individual studies and for pooled Phase 2 and Phase 3 studies. The Sponsor did not, however, analyze the data and provide conclusions. The cut off point used for scatter plot analysis, a change reported as ± 70% of the baseline value, doesn't provide an adequate assessment for a safety review. Multiple cut off points (i.e. 20%, 40% and 60%) would provide adequate study to reveal trends within the data. One cut off point which allows for significant variability within the data, doesn't offer insight into the safety of the test drug.

In brief review of the data, the following parameters were found to have outliers: Basophils, eosinophils, lymphocytes, monocytes, neutrophils, platelets, RBC, WBC, alkaline phosphatase, SGPT, LDH, total bilirubin, BUN and creatinine.

Hematology findings reveal no specific trends, however, there was variability seen in both basophil and eosinophil count data. The majority of findings were increased values, however, most values remained within the normal range. Serum Chemistry parameters did not reveal any specific trends. The majority of outliers were seen in SGOT, LDH and total bilirubin. Again most of the changes were increases from baseline. The LDH outliers had several patients with increases above the normal range at any one specific time point but no continuous increases were seen among multiple time points for individual patients. (Source: Information submitted after NDA filing with letter date 7/17/98)

Phase 1 Results: Sponsor summary

Clinical laboratory assessments, including hematology, clinical chemistry and urinalysis were performed prior to and following injection with the study agent in all four of the Phase 1 studies. As was observed in the Phase 2 & 3 studies, changes from baseline were small and not clinically relevant for all parameters in each of the four studies. There were no consistent, treatment-emergent changes observed in any of the laboratory parameters. Most changes that were noted were transient and were only slightly above or below the normal range.

In Study 10, a non-randomized, unblinded clinical trial designed to evaluate the biodistribution, accumulation, elimination and safety of Technetium Tc 99m P829 in normal healthy volunteers, three subjects, all at one study site, were noted to have low growth hormone levels at 1 hour post-injection. The decreased levels persisted through the 24 hour post-injection assessment. There was no apparent clinical significance to these changes. Given the variability evident in this measure in other subjects and the extremely short half-life of the hormone (20-25 minutes), the Sponsor concluded that experimental error in sample handling and assay may have resulted in these low values.

***Comment:** Review of study 10 revealed that all patients were fasted for a minimum of 4 hours prior to the administration of test drug, however, patients were allowed to eat a small meal approximately 2-4 hours after administration. It is known that growth hormone varies in response to fluctuations in metabolic fuels, stress and other stimuli, therefore, the meal that subjects were allowed to eat may have played a role in the decreased values reported.*

The Sponsor did not provide summary statistics for the pooled safety data collected in the Phase 1 studies.

Immunogenicity Testing:

The immunogenicity of the P829 peptide was assessed in two Phase 1 studies, 829-12 and 829-13. In both studies, baseline and 3-week post-injection plasma samples were to be obtained for analysis. A total of 18 of the 32 subjects and patients enrolled in these two studies had both pre- and post-injection samples drawn. An [redacted] was carried out to detect the presence of human IgG and IgM antibodies to P829 peptide by [redacted] None of the patients or subjects had pre-existing IgM or IgG P829-specific antibodies. The administration of P829 did not lead to the generation of human IgM or IgG P829-specific antibodies in any of the patients or subjects tested.

Reviewer's Discussion:

Depreotide was administered to both subjects and patients over the course of 3 years. The initial introduction of Depreotide in humans was in the form of the investigational, unheated formulation. As seen in Table 1, all of the Phase 1 trials, which included the initial ground work development (PK, PD, Dosimetry), were performed using the market formulation with approximately half using the heated preparation and half, the unheated preparation. A subsequent PK/PD study was performed using the market, heated formulation. Given the presence of multiple versions of formulation and dose preparation used, analysis of the data should have been performed by formulation and dose preparation. Unfortunately, the Sponsor presented an analysis based on pooled safety data, therefore, the influence of these multiple variables could not be directly assessed. The Sponsor did present pooled data in three groupings, by phase 1, by phase 3 and by phase 2 & 3. The pooled phase 2 & 3 data does weed out all those studies that utilized the investigational formulation, and the Sponsor did report adverse events by formulation, but not by dose preparation. Also, within several of the studies (22, 30A, 30B) both the heated and unheated dose preparations were used, so pooled Phase 2 & 3 data represent a combined profile for dose preparation. Not knowing if the peptide is structurally or functionally altered by the heating process, a subset review of all safety parameters should have been provided. To further substantiate the need for this breakdown, analysis of the chemistry data revealed (as per Dr. R. Harapanhalli) that a larger proportion of chemical impurities were reported with the heated dose preparation. Also, given that the pivotal trials utilized the heated, market formulation, labeling will need to reflect the safety and efficacy profile for the heated, market formulation.

When looking at the pooled adverse event data, it is seen that the Sponsor reported adverse events by number of injections rather than by total number of patients. Remembering that 911 subjects/patients were enrolled and 923 injections were administered, all percent rates for adverse events were reported based on total number of injections rather than by total number of patients. Given the small difference between the two totals, the Sponsor's results are not expected to change significantly, but a reanalysis will be needed based upon the total number of patients. Given what was presented by the Sponsor, adverse events were reported in a small number (n=49) of the total number of patients exposed (N=911). The most commonly reported adverse event was headache followed by nausea and diarrhea. The body systems, where most of the events occurred, were central and peripheral nervous systems (2%), gastrointestinal system (2%) and the body as a whole (1%). All other body systems reported the occurrence of adverse events in less than 1% of the total number of injections. Unfortunately, the Sponsor did not subset the adverse events by healthy subjects, however, given the small number of healthy subjects studied, inferences of trends may not have been identified. The majority of the adverse events were reported as mild in severity and self-limiting in nature. Within the 3 body systems where 2% of the events occurred, the following were rated as severe- one incident each of headache, diarrhea, abdominal pain, tooth pain, and malaise, and 2 incidents of back pain. All of the severe adverse events were reported in patients who received the unheated dose preparation of the to-be-marketed formulation

Approximately one fifth of the injections were administered in Europe and interestingly enough, only 2 patients reported experiencing an adverse event (lymphocytosis and endocrine disorder). Even though this sample size is small compared to the United States, a profile similar to that of the U.S. would have been expected if similar populations and procedures existed. The Sponsor does not address the difference seen. Upon a careful look at the data, most European sites were used in Phases 2 & 3 and enrolled both healthy subjects and patients.

The Sponsor's breakdown of the adverse event data by formulation does not offer much insight into any differences that may exist between the two due to the relatively small sample size that received the investigational formulation. No major differences in adverse event occurrences was seen when presented by demographics, however a slight increase in adverse event reporting was seen in the female population.

Vital sign data, as presented, did not show any clinically significant trends. The Sponsor's use of cut off points for determining clinically significant changes as compared to baseline appeared to be too liberal, however, no adverse events which would reflect direct changes in these parameters were identified. No scatter plots or shift tables for vital sign data were provided, thus limiting the analysis of this data. The mean changes from baseline showed an overall trend toward decreasing values for all vital sign parameters virtually at all time points as well. The mean changes seen, however, were slight and not found to be clinically significant. In several studies including the pivotal studies, the Sponsor collected oral body temperature data, however did not present any analysis of this data in the integrated summary of safety. Analysis of this data will need to submitted by the Sponsor.

Clinical laboratory data was collected in a majority of the clinical trials. However, the extent of the number of parameters assessed was variable. The Sponsor's integrated summary of safety only summarizes those parameters that were represented in the pivotal Phase 3 studies. In other words, parameters that were collected in earlier phases of study that weren't collected in the pivotal studies, were not summarized in the ISS. This data includes urinalysis and clinical chemistry data.

Since P829 is a somatostatin analog, it is possible that it could have similar physiologic action as native somatostatin. Given this, the Sponsor performed a study to monitor the effects of P829 on glucose levels after a glucose tolerance test (P829-10). The study looked at a small sample of mostly healthy individuals. The study results did not show any affect of P829 administration on glucose levels, however, generalizablity as to its safety in severely ill or diabetic patients cannot be concluded from this limited study. Labeling should address that the effects on glucose levels in diabeticpatients and the severely ill are unknown.

Again, as seen with vital sign data, all laboratory data was pooled regardless of dose preparation. No specific trends in the hematology and limited chemistry data were seen. Upon Division request, the Sponsor provided scatter plots for the laboratory data. Review of the outliers, does not suggest the presence of any specific trends present in the data, however, the cut off point for outlier designation was not appropriate for all laboratory parameters.. Review of the clinically significant laboratory changes did not reveal any significant trends.

All Phase 1 safety data was summarized by the Sponsor in text form. No tables of pooled data showing mean changes from baseline were presented, therefore, limited statements about this data can be made.

Immunogenicity testing performed in patients receiving a single injection revealed no reported production of IgG or IgM antibodies to the P829 peptide. No other type of immunogenicity testing was performed, such as complement activation studies, and no testing was performed on patients receiving multiple injections. The Sponsor, however, did report that no adverse events or allergic type reactions were seen in the subset of patients receiving multiple injections.

Reviewer's Conclusion: To provide a complete and accurate review, the safety data should have been broken down by dose preparation. However, since the review of the pooled data does not suggest any significant safety concerns, it is not expected that further breakdown of the data would result in any significant safety problems. For the purposes of accurate labeling, the Sponsor should respond to the following requests:

1.) Reanalysis should be performed for the following:

a.) Heated vs. Non-heated dose preparation for all safety parameters.

b.) Adverse events need to be reported by total number of patients as opposed to total number of injections.

2.) Analysis of the pooled data collected but not reported in the ISS will need to be submitted for the following Parameters:

a.) Body temperature

b.) Urinanalysis

c.) Serum chemistries: Sodium, Potassium, Chloride, Calcium, Glucose, Phosphorous, Carbon dioxide, Uric Acid, γ Glutamyl Transpeptidase, Gastrin, Thyroxine, Growth Hormone.

APPEARS THIS WAY
ON ORIGINAL

8.0 Overview Of Efficacy: (Statistician's review not complete, therefore, the reader is referred to the Statistician's review throughout this overview)

The pre-clinical studies revealed adequate data to support somatostatin receptor binding as the mechanism of action for this drug. The pre-clinical data also supports the current concept that tumors and normal tissue variably express somatostatin receptors therefore, supporting the notion that a positive Tc99m P829 image does not definitively identify malignancy and a negative Tc99m P829 image does not exclude the presence of malignancy. The inference that malignant tumors hyperexpress somatostatin receptors is not confirmed or discounted by this data. The only statement that can be made is that a tumor does or does not express somatostatin receptors based on Tc99m P829 image results as correlated with histopathology.

The data obtained from phase 1 and 2 trials in humans confirms that Tc99m P829 readily distributes within tissues of the body demonstrating adequate imaging characteristics to support continued investigation. Non-pivotal phase 3 trials (30A & B) were performed to assess the ability of Tc99m P829 to detect neuroendocrine tumors using a final institutional diagnosis as the standard of truth. The Sponsor identified limited utility for imaging the abdomen due to a biodistribution which was less than conducive to imaging, thought to be related to the drug's route of excretion. Thus, a regional analysis, in particular the region of thorax, was thought to offer the best venue upon which to test the drug's effectiveness. Given this knowledge, the pivotal studies were designed to assess the ability of Tc99m P829 to image tumors of the lung. The design of the trial provided for histopathology as the standard of truth upon which to compare the Tc99m P829 image results. In these trials, it was intended to show the presence of somatostatin receptors on all tumor biopsied, however, limitations of the amount of tissue recovered at biopsy resulted in insufficient tissue for in vitro receptor binding assays. A small number of biopsies were tested in study 34A. The findings resulted in confirmation of the presence of somatostatin receptors on both malignant (adenocarcinoma, squamous cell cancer and large cell cancer) and non-malignant (granuloma) tumors. This data also showed that tumor positive for somatostatin receptors had no detectable P829 binding. This finding may be related to the technical aspects of the assay, however, this has not been substantiated. Variability of somatostatin receptor expression between tumor type and within tumor will limit the usefulness of this agent. For this reason, the use of Tc99m P829 for staging purposes is not appropriate.

A pivotal study design flaw was identified. This flaw is related to the ability of the Sponsor to confirm consistency of tumor localization so that each diagnostic test, utilized in the study, appropriately identified the same lesion. Effectiveness of this drug depends on the consistency of this localization and, therefore, an appropriate lesion tracking system needed to be instituted. Lesion localization was identified at the time of enrollment based on CT and or chest X-ray findings. Lesions were defined by region only. No description of the lesion or landmarks were used to more specifically denote the anatomical location of the lesion. The region identified at enrollment became the region upon which all other diagnostic test were studied. No comment regarding the presence of multiple lesions within one region was made either.

The ability of the Sponsor to show, without doubt, that the lesion biopsied was the same lesion seen on Tc99m P829 was critical. In review of the data, of the 226 evaluable patients from the pivotal studies, 127 (56%) were reported as presenting with a solitary pulmonary nodule, thus suggesting that in over half the population this issue of localization may not have been a concern. However, in review of those 41 patients where discrepancies were noted and where the adjacent region algorithm resolved the issue, 22 patients presented with a solitary pulmonary nodule. The fact that patients with a single lesion still had discrepancies in localization may show the inherent inaccuracies of the diagnostic imaging modalities in localizing lesions for biopsy. In the 44% of the patient population that did not present with a SPN, this may or may not have been an issue. The Sponsor stated that the enrolling CT was, in most cases, what directed biopsy, therefore, it is anticipated that lesion localization, as far as the biopsy is considered, was appropriate (the majority of biopsies were needle biopsies). Specific anatomical localization of the lesion by Tc99m P829 is not practical given the anatomical resolution of nuclear medicine imaging in general. The Sponsor did perform SPECT imaging which would allow for the optimal localization given the diagnostic modality. All in all, the localization system used was by no means perfect and the resulting problems were a result of imprecision of both man and machine. Given that the discrepancies seemed to involve a small percentage of the total population, it does not appear that tracking was a significant problem. Given all this, the most accurate means to support efficacy is through the one-to-one analysis, therefore, that is what is recommended in support of efficacy for this NDA.

Multiple protocol violations and deviations were identified over the course of execution of the pivotal trials. The violation of biopsy prior to enrollment was initially thought to have potential impact on the outcome of the trial, however, review of the study report shows that the utility of this agent does not lie in it's ability to function on its own as a diagnsotic screening tool. Enrolling 42% of the patients with known cancer rather than suspicious for cancer does not bias the comparison of the blinded Tc99m P829 image results when compared to histopathology. The issue that the biopsy procedure itself, when performed prior to imaging, may impact the image results (uptake resulting from inflammation rather than tumor binding)is resolved by the similar specificity calculations seen for the groups with biopsy prior to and biopsy after Tc 99m P829 imaging.

The primary efficacy analysis consisted of sensitivity and specificity calculations for Tc99m P829 images results when compared to histopathology results for identification of a benign versus malignant disease process. After an initial intent-to-treat analysis using a one-to-one correspondence for lesion identification, the Sponsor reported discrepancies in Tc99m P829 localization as compared to histopathology localization. The Sponsor further reported that Tc99m P829 imaging often identified uptake in adjacent regions to the region identified by biopsy. In order to adjust for this occurrence the Sponsor performed efficacy analyses using an adjacent region algorithm.

This algorithm allowed agreement to be conferred if Tc99m P829 was in the general vicinity of the lesion localized by histopathology. This discrepancy further stresses the need for an adequate tracking system to limit this occurrence, realizing of course, that this cannot be totally eradicated given the limitations of all the diagnostic modalities involved. Given the limited tracking system utilized by the Sponsor, this reviewer has chosen to present the one-to-one analysis in support of this NDA.

The Sponsor's sensitivity, specificity and agreement results per majority blinded read for the one-to-one algorithm analysis are reported below (Table 1).

Table 1. Primary Efficacy Analysis for the One-to-One Algorithm Analysis per Study

	MAJORITY BLINDED READ			
	Sensitivity	Specificity	Accuracy	N
Study A	70%	86%	74%	112
Study B	71%	79%	72%	114
Combined	71%	83%	73%	226

The tumor types studied which localized Tc99m P829 include adenocarcinoma, squamous cell, small cell, large cell, carcinoid and non-small cell cancer of the lung. Of those benign lesions studied, granulomatous and other inflammatory processes were found to concentrate Tc99m P829. Of the false negative cases reported, the Sponsor offered several explanations as to the reason for non-visualizing these on Tc99m P829. The difficulty in visualization was subdivided into 5 categories: location of lesion near a rib, size of lesion (smaller lesions were more difficult to detect) presence of diffuse uptake in diseased lungs, presence of multiple lesions and technical issues. These categories did not definitively support the reason for the false negative results seen. In cases where location of the lesion was cited as the reason, it appears as though a lack of adequate target to non-target ratios resulted in the false negative result. This finding could be more a factor of the binding of the drug rather than the location of the lesion. The argument about size of lesion is a valid one, however, large tumors were reported as falsely negative. Again, this is an issue of poor concentration of the tumor with Tc99m P829. Regardless of the Sponsor's reasoning for the false negative cases, this drug's anticipated mechanism of action, binding to somatostatin receptors, will always have an affect on the efficacy of this drug. Poor receptor expression will result in poor tumor concentration of the drug.

A subgroup analysis on those patients who presented with a solitary pulmonary nodule was performed as a secondary analysis. Results suggest poor sensitivity and specificity with lesions between 1-3 cm in size. The accuracy of the diagnosis of solitary pulmonary nodule, made at the time of enrollment, is in question, therefore, the results of this analysis will not be considered in labeling.

Sensitivity and specificity calculations performed for CT as compared to histopathology reveals excellent sensitivity but poor specificity with CT. These findings were not unexpected. When sensitivity and specificity of P829 is compared to CT, it is found that the specificity dramatically improves with the use of Tc99m P829. This finding suggests that Tc99m P829 when used in conjunction with CT may offer useful information regarding the presence or absence of malignancy. A comparison of the potential diagnostic information provided by Tc99m P829 when used in conjunction with CT can be found in Table 2.

Table 2. Diagnostic Capacity of Images/Cscans Taken Together (Studies 34A and 34B Combined)

	One-to-One Algorithm	
	H=0	H=1
CMAJ=0 IMAJ=0	8	7
CMAJ=0 IMAJ=1	3	6
CMAJ=1 IMAJ=0	27	47
CMAJ=1 IMAJ=1	4	124

Data Source: Modification of FDA Statistician's Table VII. CMAJ= majority blinded CT read, IMAJ= majority Blinded Tc99m P829 image read, H=0: histopathology negative for malignancy, H=1: Histopathology positive for malignancy.

The results of this analysis show that Tc99m P829 may offer useful information to a clinician when both the CT and Tc99m P829 studies are both positive. In this case, it appears that a positive Tc99m P829 improves the likelihood of the tumor being malignant rather than benign. There was no relationship seen for confirmation of benign disease when both CT and Tc99m P829 were both negative.

It is important to remember that somatostatin receptors are present on the surface of benign and malignant tissues and are variably expressed by tumors, therefore, interpretation of Tc99m P829 findings should be made with caution and in context with all other clinical findings.

The ability of this drug to accurately aid in the staging of disease has not been adequately supported.

The clinical usefulness that this drug is not fully appreciated. It is anticipated that positive Tc99m P829 images in a select patient population (those with abnormal CT scans) may influence the selection of lesion for biopsy by identifying lesions suspected of being malignant due to their uptake of Tc99m P829 or influence the timing of biopsy. It is not felt that this drug should in anyway preclude the need for biopsy when CT results are abnormal.

Non-scientific issues: Issues surrounding the completeness and accuracy of the pivotal data were identified over the course of the review. In particular, lack of reporting protocol violations which had potential impact on efficacy results were identified, inconsistencies in biopsy dates were found and extensive deviations from the protocol were reported. The impact that these issues have on the outcome of this review is not fully appreciated. Inspection of two clinical sites by the Division of Scientific Investigations did not identify any violation of pertinent Federal regulations or good clinical investigational practices. Review of the protocol violations that were underreported by the Sponsor did not show any significant effect on the efficacy analysis.

Conclusions: Given the that this is the second somatostatin analogue to be reviewed for diagnostic purposes, the concept of the mechanism of action of the binding of this drug to somatostatin receptors is not foreign. There is adequate data to support the approval of Tc99m P829 for aiding in the detection of lung tumors which express somatostatin receptors in patients with a high likelihood of disease when used in conjunction with computed tomography. The limited patient population for which this drug is useful must be addressed in labeling. It is not felt that this drug should in anyway preclude the need for biopsy when CT results are abnormal.

Follow-up studies to further investigate the potential specificity of this drug for one tumor type over another (which may be related to subtype of somatostatin receptor expressed and/or affinity of Tc99m P829 for that receptor) may offer poignant clinical utility. Also further investigation as to the potential affect of prior treatment (i.e. radiation and/or chemotherapy) on the biodistribution of Tc99m P829 and its specific binding to somatostatin receptors should be addressed.

9.0 Reviewer's Conclusion:

Safety:

To provide a complete and accurate review, the safety data should have been broken down by dose preparation. However, since the review of the pooled data does not suggest any significant safety concerns, it is not expected that further breakdown of the data would result in any significant safety problems. For the purposes of accurate labeling, however, the Sponsor should respond to the following requests:

1.) Reanalysis should be performed for the following:

[redacted]

b.) Adverse events need to be reported by total number of patients as opposed to total number of injections.

2.) Pooled analysis of the data collected but not reported in the ISS will need to be submitted for the following parameters:

a.) Body temperature

b.) Urinanalysis

c.) Serum chemistries: Sodium, Potassium, Chloride, Calcium, Glucose, Phosphorous, Carbon dioxide, Uric Acid, γ Glutamyl Transpeptidase, Gastrin, Thyroxine, Growth Hormone.

Efficacy:

Given that this is the second somatostatin analogue to be reviewed for diagnostic purposes, the concept of the mechanism of action of the binding of this drug to somatostatin receptors is not foreign. There is adequate data to support the approval of Tc99m P829 for aiding in the detection of malignant lung tumors which express somatostatin receptors when used in conjunction with computed tomography. The limited patient population for which this drug is useful must be addressed in labeling. It is not felt that this drug should in anyway preclude the need for biopsy.

Follow-up studies to further investigate the potential specificity of this drug for one tumor type over another (which may be related to subtype of somatostatin receptor expressed and/or affinity of Tc99m P829 for that receptor) may offer poignant clinical utility. Also further investigation as to the potential affect of prior treatment (i.e. radiation and/or chemotherapy) on the biodistribution of Tc99m P829 and its specific binding to somatostatin receptors should be addressed.

The Sponsor will need to address the inconsistencies that were documented in the pivotal studies involving protocol violations/deviations, biopsy dates and results and discrepancies seen with the application of the definition of solitary pulmonary nodule.

10.0 Recommendations:

The recommendation of approvable is made pending submission and review of the above safety data requests.

[redacted]

/S/

Sally A. Loewke, M.D.
Medical Officer

12/3/98

cc: IND Archive
HFD-160 Div. File
HFD-160/ C. Ferre-Hockensmith
HFD-160/S.Loewke

APPEARS THIS WAY
ON ORIGINAL

I agree with Dr. Loewke's review and conclusions that this NDA is approvable.

/S/ 12/4/98

A. E. Jones, M.D.
Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

cc: IND Archive
HFD-160 Div. File
HFD-160/ C. Ferre-Hockensmith
HFD-160/S.Loewke

Phase 1
Study P829-10

11.0 Supportive Studies

11.1 Study P829-10

Phase 1, P829-10: (Volumes 1.28-1.30)
Study Period: August 21, 1995 to February 29, 1996
Formulation: [redacted] Market Formulation
Population: Healthy volunteers

Phase 1 Clinical Trial Evaluating the Safety and Tolerance of Technetium Tc99m P829 in the Detection and Localization of Somatostatin Receptor-Expressing Tumors in Normal Volunteers.

Objectives:

1.) To study the overall safety and tolerance in human subjects.

2.) To study the biodistribution, uptake and clearance half-times, and routes of elimination in normal volunteers in order to determine human dosimetry and pharmacokinetics.

Design: This is a phase 1, non-randomized, unblinded clinical trial enrolling normal human volunteers for the purpose of determining the radiation dosimetry and pharmacokinetics of Tc99m P829. Ten to fifteen volunteers will receive a dose of 10mCi Tc99m P829 (50μg of peptide) followed by a saline flush after fasting for at least 4 hours. All volunteers must be 18 years or older, be non-pregnant, in good health and sign a consent form. Any volunteers taking other investigational drugs, have a history of gallbladder disease or taking anti-diabetic agents or thyroid medication will be excluded. Following intravenous administration of test drug, whole body scans will be obtained in the anterior and posterior views at the following timepoints: 10 min, 1hr, 2hr, 4hr, and 18-24 hours. Radiation dose estimates will be calculated using the MIRD schema. Blood and urine will be collected to determine radiation clearance (see Table 1 below). Safety will be assessed by monitoring vital signs, hematology, blood and urine chemistry parameters, immunologic parameters and adverse events. One pre- and two post-injection (4 and 24 hr) questionnaires will be completed by each subject to elucidate a side-effect profile. No statistical analysis plan for the safety data were given.

Table 1. Time Table of Events

	Assessment						
Time	Blood Radioactivity	Vital Signs	Hematology, Urine Chemistry & Blood Chemistry	Urine Radioactivity	Whole Body Imaging	Immune Response	Symptom Questionnaire
-1 hr to 0		X	X			X	X
1 min	X						
2 min	X						
3 min	X						
4 min	X						
5 min	X	X					
10 min	X				X		
15 min	X						
30 min	X	X					
1 hr	X	X	X	X	X		
2 hr	X	X		X	X		
4 hr	X	X	X	X	X		X
8 hr				X			
18-24 hr	X	X	X	X	X		X
3 weeks						X	

Note: Time 0 represents the time of administration of Technetium Tc 99m P829.

There were no protocol amendments.

Dose: Doses will be prepared from nonradioactive kits. Each vial was reconstituted with 1ml of Sodium Pertechnetate Tc99m. The vial will be swirled and allowed to sit at room temperature for 15 minutes. Radiolabeling efficiency will be tested and only doses with > 85% of Technetium 99m activity as Technetium 99m P829 will be used. Each subject is to receive a single IV administration of 10mCi Tc99m P829 (50μg). The dose can be diluted to a convenient injection volume using 0.9% sodium Chloride Solution.

Results:

Protocol deviations are as follows:

1.) Blood samples for the assessment of immune response were not collected.

2.) Complete dosimetry analysis was not performed. The radiation dosimetry for P829 was to be collected in a separate study.

3.) There was a failure to record measurement times for vital signs for all subjects at Site 2.

4.) There was a failure to obtain blood and urine clearance data and whole body imaging for Subjects 829-10-02-06 and 829-10-02-07.

5.) There was a failure to record P829 peptide dose for Subjects 829-10-02-06 and 829-10-02-07.

Table 3. Biodistribution-Mean Percent Administered Dose Per Organ

Organ	Statistic	Post-Injection Evaluation Time				
		10 min	1 hour	2 hours	4 hours	18-24 hours
Whole body	n	15	15	15	15	15
	Mean %	98.43	97.38	96.67	93.55	105.25
Lung	n	15	13	10	9	5
	Mean %	6.12	5.32	4.57	4.34	2.87
Thyroid	n	10	7	7	7	6
	Mean %	0.79	0.84	0.76	0.76	0.63
Liver	n	15	15	15	15	15
	Mean %	10.54	10.30	10.59	11.64	10.70
Kidney	n	15	15	15	15	15
	Mean %	13.01	14.65	14.96	15.56	16.26
Bladder	n	13	13	13	8	5
	Mean %	1.81	1.93	1.68	1.34	1.48
Spleen	n	15	15	15	15	15
	Mean %	4.05	4.02	4.02	3.43	4.09
Colon	n	14	14	15	15	15
	Mean %	4.15	5.68	5.92	7.15	6.73
Pelvic Area	n	15	15	12	10	12
	Mean %	6.29	6.15	6.50	6.50	7.19

Data Source: Section 14.2, Table 9.0, Sponsor text table 5-A.

Comment: A complete analysis including organ residence times, radiation dose estimates, effective dose equivalent and effective dose were not performed. Therefore, the radiation absorbed doses to the critical organ and target organ are not available from the study report. It was found that the kidney plays only a minor role in the excretion of Tc99m P829, however, feces samples were not collected to account for other modes of excretion.

Pharmacokinetics: (See Biopharm review)

Pharmacokinetic modeling of blood radioactivity levels after Technetium Tc 99m P829 administration indicated triphasic decay, with a rapid decline in radioactivity soon after administration (median half-life of 3.7 min), followed by a more gradual decline with a half-life of 35.2 min, and a slow decline with a half-life of 17.9 h (median values). The median estimates for body weight–normalized volume of distribution at steady state (V_{ss}) and volume of distribution of the central compartment were 3.12 L/kg and 0.154 L/kg respectively, and total clearance (CL) of radioactivity was 3.89 mL/min/kg. Urinary excretion accounted for 5.3% to 7.7% of the total dose. Average renal clearance (CLR) of radioactivity was 0.255 mL/min/kg.

Disposition: Seventeen subjects were enrolled. Of the 17, 10 subjects were enrolled at Site 1 and 7 were enrolled at Site 2. All subjects met the inclusion/exclusion criteria, however, due to the protocol violations, 2 of the 17 subjects were not included in the pharmacokinetic and biodistribution analyses.

Dose: All patients received a single IV administration of 10mCi Tc99m P829. Kits used for this study were not heated. Lots used were from the to-be-marketed formulation (lot # 9509M01A and 9509M01B).

Demographics:
All 17 subjects were included in the following demographics description. Of the two subjects not included in the dosimetry and pharmacokinetic analyses, one was female weighing 57 kg and one was male weighing 80 kg.

Table 2. Demographics

Statistic	All Subjects
Gender	
Male	8
Female	9
Age (yrs)	
Mean	35.8
Range	19-64
Weight (kg)	
Mean Male	73.5
Range	59-90
Mean Female	60.6
Range	47-77

Data Source: Sponsor Tables 2.0, 2.1.

Biodistribution

Subjects underwent anterior and posterior whole-body gamma-ray scintigraphy at 10 minutes, and at approximately 1, 2, 4, and 18-24 hours after injection. Descriptive statistics were summarized for the calculated percent administered dose per organ or ROI, corrected for the physical decay of the radionuclide, for the following regions of interest: whole body, lung, thyroid, liver, kidney, bladder, spleen, colon, and pelvic area. The mean values for percent administered dose per organ are shown below in the Table 3.

Safety:

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

Extent of Exposure: A total of 17 subjects received a single administration of Tc99m P829. Actual doses of Tc99m administered ranged from 8.3-10.8mCi. Actual doses of P829 peptide administered ranged from 35-50μg. Only doses with radiochemical purity of greater than 85% were administered.

Adverse events: Three subjects experienced a total of 5 adverse events (Table 4). Subject number 7 experienced three events including rigors, increased sweating and syncope approximately 50 minutes post administration. The Sponsor noted that the patient fainted in the restroom after urinating and felt this was a vasovagal response and therefore, not related to the test drug. Subject 9 experienced backpain felt to be related to lying supine for the imaging. Subject 9 also experienced nausea and vomiting but had these symptoms prior to test drug administration, therefore, this was not deemed as drug related.

Table 4. Table of Adverse Events

Subject Number	Adverse Event	Preferred Term	Injection Time	Onset	Severity	Dose mCi	mcg
7(Site 1)	Fainting	Syncope	9:40am	10:30am	Mild	10.27	40
7	Chills	Rigors	9:40am	10:30am	Mild		
7	Sweating	Increased sweating	9:40am	10:30am	Mild		
9	Backache	Backpain	9:10am	11:00am	Mild	9.77	40
9	Nausea/Vomiting		9:10am	pre-inj*			
1(Site 2)	Metallic Taste	Taste Perversion	10:47am	14:45pm	Mild	10.48	50

Data Source: Sponsor Table 10.0, Appendices 16.2.5, 16.2.8
*subject 9 had nausea and vomiting pre-drug administration as well as post administration.

Comment: Patient 1-7 had stable systolic and diastolic blood pressures recorded at al timepoints. Pulse was found to decrease slightly at the at the 5 minutes assessment and again at the 1 hour assessment. Pulse decreased immediately at the 5 minute assessment and remained stable for the remainder of the assessments. Temperature also remained stable. Causal relationship to the study drug cannot be excluded.

Laboratory Data:

Potassium: Three subjects were noted to have mild elevations of potassium within one hour post drug administration. In each case, the potassium levels returned to normal by the 24 hour assessment.

LDH: Four subjects had mild to moderate elevations of LDH levels occurring within the first 4 hours after drug administration. Each elevation did not persist and in all cases but one, returned to normal range by the subsequent assessment. One subject, out of the four, had an accompanied elevation in SGOT, but this was very mild and did not persist.
Growth Hormone: Three subjects (all females) had decreases in growth hormone levels when compared to baseline and in all cases the levels remained below normal up to 24 hours post-drug administration.

Comment: *Growth hormone varies in response to fluctuations in metabolic fuels , stress and other stimuli. All patients were fasted for a minimum of 4 hours prior to the administration of test drug. Patients were allowed to eat a small meal approximately 2-4 hours after administration and it is known that a glucose load (as occurs after eating a normal meal) suppresses growth hormone. No definite correlation to test drug can be made based on this data alone.*

Glucose: There were several fluctuations in glucose levels most of which were increases at the 4 hour assessment. As part of the protocol, subjects were allowed to eat a light meal between 2 and 4 hours after drug administration and it is anticipated by the Sponsor that food consumption may have affected the post-injection blood glucose values. In all but two cases, the levels returned to normal by the 24 hour assessment. The two cases that did not, where subjects that had levels below the normal range at 24 hours.

Vital Signs: Blood pressure, respiration, pulse and temperature show no clinically significant trends.

Pulse: One patient as identified by the Sponsor had a drop in pulse from a baseline value of 82 bpm to a 5 minute value of 64 bpm. The subjects pulse rate rose to 76 bpm at the 30 minute assessment and no adverse events were reported at this time.

Comment: The Sponsor has no time recordings for vital sign assessments for subjects at Site 2. The comparability of the vital sign assessments between subjects at site 1 and 2 is compromised without proper documentation of the times the assessments were taken. Looking at the sites individually, however, there does not appear to be any clinically significant trends.

Sponsor's Conclusions:

Pharmacokinetics:

Blood radioactivity levels after Technetium Tc 99m P829 administration exhibited triphasic decay, with a rapid decline in radioactivity soon after administration (median half-life of 3.7 min), followed by a more gradual decline with a half-life of 35.2min, and a slow decline with a half-life of 17.9 h (median values).

The median estimates for body weight-normalized volume of distribution at steady state (V_{ss}) and total clearance (CL) of Technetium Tc 99m P829 were 3.12 L/kg and 3.89 mL/min/kg, respectively. Given an average subject body weight of 66 kg in this study, the value of V_{ss} suggests that there is significant distribution into body tissues. Urinary excretion accounted for 5.3% to 7.7% of the total dose, and average renal clearance CLR was 0.255 mL/min/kg, indicating that the kidney plays only a minor role in the excretion of Tc 99m P829.

Biodistribution: The greatest activity is found in the kidneys, liver, pelvic region and lung.

Safety: A single IV injection of Technetium Tc99m P829 was well-tolerated and safe In healthy volunteer subjects. Adverse events were infrequent, and no adverse events were judged as related to the administration of the study agent. Changes in vital signs and laboratory data were transient in nature and not considered clinically significant. The dose was safe and well-tolerated.

Reviewer's Discussion: The design of this study did not provide for the analyses of radiation dosimetry and pharmacokinetic data for the parent peptide. These two missing pieces are essential to the fundamental understanding of the drugs safety. The reasons for lack of these analyses are not clearly delineated within the study report however, the Sponsor does state that radiation dosimetry was investigated in a subsequent study.

The PK data resulting from this study illustrate two points of concern: 1.) The relatively long terminal half life (20hr) of this drug and 2.) The minimal amount excreted by the kidney and the lack of investigation as to the route of excretion. These issues pose serious questions regarding the radiation dose to both the target and critical organs and may be addressed in subsequent studies.

The Sponsor distributed a questionnaire with a list of possible adverse events and had the subject circle yes or no as to whether they experienced these symptoms or not. The Sponsor did provide a space for other conditions experienced on the questionnaire. It is unclear if the Sponsor, during the first hour post dose, verbally asked subjects for the presence or absence of adverse events. These questionnaires, may have misled the subjects into thinking that these were the only types of symptoms that may accompany the use of this drug and may have led to under reporting of adverse events even though the "other" category was listed on the questionnaire. A general question posed to the patient regarding the presence of side-effects would have been preferable.

Of those side effects reported, one subject experienced three events: chills sweating and fainting. The Sponsor interpreted this as a vasovagal response to "blood and the indwelling catheter". No changes in blood pressure and temperature were seen at the time of this incident. There was a drop in pulse and respiration rate seen at 5 minutes post dose which extended past the 1 hour assessment. The baseline pulse was 72 bpm and dropped to 60 bpm at the 5 minute assessment and further dropped to 56 bpm at the one hour assessment. The respiration rate at baseline was 20 and dropped to 16 bpm at 5 minutes and continued at this level for the remainder of the study. The relationship of this event to the study drug is not conclusive. All other adverse events were mild and self-limiting.

Review of the laboratory data shows elevations of LDH in subjects within the first 4 hours post dose with return to normal levels by 24 hours. In all cases but one, no other liver function tests were abnormal.

Growth hormone varies in response to fluctuations in metabolic fuels, stress and other stimuli. All patients were fasted for a minimum of 4 hours prior to the administration of test drug. Patients were allowed to eat a small meal approximately 2-4 hours after administration and it is known that a glucose load (as occurs after eating a normal meal) suppresses growth hormone. No definite correlation to test drug can be made based on this data alone.

Vital sign assessments did not show any clinically significant trends. However, at Site 2, the investigator failed to record the time at which point the vital sign measurements were taken, therefore, it prevents combining the results of both study sites. An cursory review of vital signs for the individual sites did not show any clinically significant trends.

This study utilized the [redacted] dose preparation of the market formulation. The phase 3 protocol which supports the efficacy of this drug, utilized the [redacted] dose preparation of the market formulation. [redacted]

Reviewer's Conclusions:

1.) Further study is needed regarding the Pharmacokinetics and radiation dosimetry for this drug as the data provided here is not sufficient. **Note:** Review of the Division file revealed a medical officer review of IND [redacted] which provides the MIRD absorbed dose calculation for this study. The Sponsor did not supply this information as part of the NDA.

2.) Within this small sample of healthy volunteers, the administration of Tc99m P829 appears to be safe. [redacted]

Phase 1
Study P829-11

11.2 Study P829-11

Phase 1, P829-11 (volumes 1.79, additional Information submitted after Filing -Letter Dates 7/9/98 and 8/26/98.)
Date of Study: August 1, 1996 to November 1, 1996
Formulation: [redacted] Market Formulation
Population: Healthy Volunteers

Phase 1 Clinical Trial to Evaluate the Safety, Tolerance and Normal Imaging Patterns of Technetium Tc99m P829 in Normal Volunteers.

Objectives:
1) To evaluate Technetium Tc 99m P829 for safety and tolerance in normal volunteers;
2) To evaluate the imaging patterns of Technetium Tc 99m P829 in normal volunteers, using SPECT and focal planar images of the abdomen and thorax; and
3) To provide normal images for later inclusion in blinded evaluations of images obtained of subjects with tumors for a later study.

Design: This is a multicenter, non-randomized, open-label Phase 1 study to evaluate the safety and normal imaging patterns of Tc 99m P829 ([redacted] market formulation) in normal healthy volunteers over the age of 18 years. Each subject will receive a single intravenous injection of 20mCi of Tc99m P829 (50µg of P829 peptide) after fasting for at least 4 hours. Focal planar and SPECT images of the thorax and abdomen will be taken at approximately 1 and 3-6 hours post-injection. Images from this study will be combined with images from study P829-30 and will be randomly read at a core laboratory by three blinded Nuclear Medicine physicians. No specific efficacy analysis is intended and blinded reader case report forms were not provided. Safety monitoring will include vital sign assessment, clinical laboratory assessment, urinalysis and adverse event reporting. Table 1 provides information regarding the timing of procedural events.

Table 1. Timing of Procedures

	Pre-Study	Post-Study					
Procedure		**5 min.**	**30 min.**	**60 min.**	**1 hr**	**3-6 hr.**	**18-24 hr.**
Consent	√						
Vitals	√	√	√	√		√	√
Labs	√				√	√	√
Urinalysis					√	√	√
Symptom Questionnaire	√					√	√
Imaging					√	√	

Results:

Protocol Deviations: Subjects at study site 3 received lower activity doses than what was proposed in the study protocol. The net activity administered at site 3 was 8.71 to 9.57 mCi.

Disposition: Twenty normal subjects were enrolled at 4 clinical sites, 5 subjects per site. All 20 subjects received a single administration of study drug and completed the study.

Demographics: Please see Tables 2 and 3 for demographic characteristics.

Table 2. Demographics

Parameter	All Subjects
Total	20
Age (yrs)	
Mean	34.5
Min.	19
Max.	50
Gender	
Male	13 (65%)
Female	7 (35%)
Race	
Caucasian	15
Hispanic	2
Oriental	2
Other	1

Data Source: Table 2.0, Vol. 1.79, pg. 049.

Table 3. Demographics

Parameter	Male	Female
Weight (kg)		
Mean	86	65
Min.	61	52
Max.	120	84
Height (cm)		
Mean	176	166
Min.	165	152
Max.	191	175

Data Source: Table 2.1, Vol. 1.79, pg. 050.

Efficacy: The Sponsor stated that no efficacy evaluation was planned for, therefore, no results were reported.

Comment: In the protocol a blinded read of the images was planned, however, the Sponsor indicated that the images from this study would be combined with images from another study, P829-30.

Safety:

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

Extent of Exposure: Twenty subjects received a single dose of Tc99m P829. The net activity administered to subjects at study site 3 was 8.71 to 9.57 mCi. The net activity administered to the remainder of the population (15 patients) ranged from 13.6 to 21.1 mCi. Twelve of the 15 received doses above 17 mCi. Only doses with ≥ 90% of radiochemical purity were administered. The Sponsor stated that subjects received approximately 50μg of P829 peptide. Lot numbers used for this study could not be found in the study report.

Adverse Events: Four subjects reported one or more adverse events. Subject 1-01 experienced three adverse events: headache, backpain and leg pain. This same subject experienced headache at two different times post-drug administration. In all cases the symptoms resolved without treatment. Three other subjects experienced one adverse event each. Those adverse events reported were backpain, fatigue and somnolence and all were self-limiting. Time of onset for two adverse events was reported as unknown. See Table 4 for complete listing of adverse events.

Table 4. Adverse Events

Patient	Adverse Event	Body System	Time of Onset Post-Dose	Duration	Severity	Relationship to study drug	Treatment Required
1-1	Headache	CNS and PNS	40 mins.	2 hrs.	mild	Probably Not Related	No
	Backpain	Body as a Whole	3.5 hrs.	Unknown	severe	Probably Not Related	No
	Leg Pain	Body as a Whole	3.5 hrs.	Unknown	mild	Probably Not Related	No
	Headache	CNS and PNS	3.5 hrs.	Unknown	Severe	Probably Not Related	No
1-2	Backpain	Body as a Whole	4 hrs.	1.5 hrs.	Severe	Probably Not Related	No
1-3	Fatigue	Body as a Whole	Unknown	Unknown	Mild	Probably Not Related	No
2-3	Somnolence	Psychiatric	Unknown	Unknown	Mild	Probably Not Related	No

Data Source: Appendix 16.2.5 and 16.2.7, Vol. 1.79, page 0219 and 0230.

The 2 subjects who had abnormal WBC values had a shift from normal baseline values to high post injection values at the 1 hour timepoint. Of the remaining 5 subjects with abnormal RBC values, 3 subjects had decrease and 2 subjects had increased post-injection values. Of the remaining 5 subjects with abnormal monocytes values, 4 had decreases and one subject had an increased value. Of the 2 subjects with abnormal hemoglobin values, one subject had a decrease and one had an increase.
Of the 5 subjects with abnormal neutrophil counts, 4 had increased counts and one had a decrease in counts. The remaining subject with an abnormal lymphocyte count had a decrease in counts.

For all the abnormal laboratory changes reported, no one subject had consistently elevated or decreased values across all timepoints. No clinically significant changes or trends were seen in the data for hematology.

Serum Chemistry: Laboratory values reported as outside of the normal ranges for more than one subject were reported for the following parameters: ALT (2), BUN (2) LDH (7), Alk Phos (5), T. Bili. (3). Of these subjects with abnormal values, a majority of the values were found to be abnormal at baseline and thus the post injection values remained consistent with the abnormal baseline value. Statistically significant changes were noted for AST, LDH, BUN and creatinine. In all cases, the changes were noted to be overall decreases and therefore are not considered clinically significant. No clinically significant trends were seen in the serum chemistry data.

Urinalysis: Statistically significant changes were noted for specific gravity at 1 hour and 3-6 hours post-injection, however, this did not appear to be clinically significant. Shift table analysis reported 2 subjects with a shift in ketone levels from normal to high. No other clinically significant trends were identified.

Vital Signs: A statistically significant mean change from baseline occurred for Systolic blood pressure at the 5 minute timepoint. However, only one Subject was found to have a clinically significant drop in systolic blood pressure over the course of this study. This subject(1-04) had a baseline blood pressure of 155mmHg which subsequently decreased to post injection values as follows: 140mmHg /5 minute, 145 mmHg/30 min., 135mmHg/1hr., 115mmHg/ 3-6 hr., and 125mmHg/18-24 hr. There was no clinically significant changes in diastolic pressures or other vital sign parameters for this subject. No other clinically significant trends were seen.

Sponsor's Safety Conclusions: The safety data suggest that Technetium Tc 99m P829 was well-tolerated by all subjects in this study.

Reviewer's Discussion:
Efficacy: The Sponsor planned to blindly read the Tc99m P829 images, however, reported that they would be read in conjunction with another study (P829-30). Therefore, the Sponsor did not report any efficacy results in this study report.

Safety:

Of the adverse events reported, it is possible to attribute the backpain and leg pain to the imaging procedure rather than to the drug. In both subjects, this pain was reported during the time of the imaging procedure. Backpain and leg pain are common complaints when subjects are asked to lie on their back for extended periods of time. The report of headache was reported within 40 minutes of injection and again at 3.5 hours and may be related to the study drug. The patient experienced a rise in blood pressure with the onset of the second episode of headache.

The other two remaining adverse events fatigue and somnolence, did not have time of onset reported, therefore, a temporal relationship to study drug cannot be established. Without any evidence to suggest otherwise, these adverse events may be related to study drug.

In most cases, all symptoms reported by subjects on the symptom questionnaire were reported as an adverse event. Two symptoms (nasal congestion and general discomfort) were not reported as adverse events. In the case of nasal congestion, it was reported on the baseline questionnaires well as a follow-up questionnaire, therefore, establishing it as a pre-existing condition and not study drug related..

There were no clinically significant trends seen in the laboratory or vital sign data.

This study utilized the [redacted] dose preparation of the market formulation. The phase 3 protocol which supports the efficacy of this drug, utilized the [redacted] dose preparation of the market formulation. [redacted]

Reviewer's Conclusions:

1.) The blinded image results for this study need to be summarized separately from Study P829-30.

2.) The [redacted] market formulation of Tc99m P829 appeared to be tolerated by all healthy volunteers in this study. One patient experienced an elevation of blood pressure with an accompanying headache.

[redacted]

APPEARS THIS WAY
ON ORIGINAL