

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021012

MEDICAL REVIEW(S)

DIVISION DIRECTOR MEMO TO THE FILE

NDA: 21,012
DRUG: NEOTECT™ (Kit for the preparation of Tc99m Depreotide Injection)
ROUTE: Intravenous Injection
MODALITY: Single Photon Emission Tomography (SPECT)
INDICATION: Imaging of Somatostatin Bearing Lung Tumors
SPONSOR: Diatide, Inc.
SUBMITTED: February 8, 1999 (Complete response)
PDUFA DATE: August 8, 1999
COMPLETED: July 22, 1999

RELATED DRUGS: OctreoScan (an ¹¹¹Indium labeled synthetic somatostatin analogue approved for imaging neuroendocrine tumors that bear somatostatin receptors)
Sandostatin (a synthetic somatostatin analogue approved to treat neuroendocrine tumors)

RELATED REVIEWS: Chemistry: Ravi Harapanhalli, Ph.D - 10/26/98, 6/23/99
Clinical: Sally Loewke, M.D. - 12/3/98, 6/7/99, 7/15/99
Microbiology: Paul Stinavage, Ph.D. - 11/18/98, 2/16/99
Pharmacology: Dave Bailey, Ph.D. - 11/6/98, 5/20/99
Pharmacokinetics: Young Moon Choi, Ph.D - 11/17/98
Alfredo Sancho, Ph.D - 6/4/99, 7/15/99
Statistics: Tony Mucci, Ph.D. - 11/23/99, 7/22/99
Project Manager: James Moore, R.Ph.

BACKGROUND: NeoTect (Kit for the Preparation of Technetium Tc99m Depreotide) Injection is a diagnostic radiopharmaceutical for imaging of somatostatin receptor bearing tumors of the lung. Diatide, Inc. originally submitted the NDA on June 16, 1998. It was reviewed as a priority drug because of its potential to assist in the diagnosis of malignant disorders and to provide the first receptor binding diagnostic information in the lung. An approvable letter was issued on December 16, 1998 with a revised indication "as a scintigraphic imaging agent indicated to identify somatostatin receptor bearing pulmonary masses in patients who are highly suspect for malignancy and have pulmonary lesions on computed tomography". The approval letter contained a number of deficiencies in chemistry, microbiology, pharmacology, human biopharmaceutics, and clinical/statistics. A response to the approvable letter was submitted partially on January 21, 1999 and completely on February 8, 1999.

Notably the sponsor's response contains a request to reinstate their proposed indication of identifying malignant pulmonary masses, and to include a clinical trials table that suggests the superiority of NeoTect with either computed tomography (CT) or chest x-ray over CT alone. This request was considered by the clinical and statistical reviewers with the conclusion that the indication should remain essentially unchanged and that a superiority claim is not justified at this time. The rationale for this decision is discussed in their reviews and under the clinical section of this memorandum.

The other issues identified in the approvable letter were adequately addressed by Diatide and all reviewers recommend approval with label revisions. These issues will be noted briefly below.

CHEMISTRY:

NeoTect is provided in a sterile solution for intravenous injection. The molecular formula is $C_{65}H_{96}N_{16}O_{12}S_2$; the molecular weight is 1357.7.

Also, the *labeling has been revised* to include a precaution on the use of depreotide with total parenteral nutrition admixtures. (A precipitate of glycosyldepreotide may form).

A pre-approval inspection was acceptable on Sept 14, 1998. The methods validation package is pending as per CDER policy.

MICROBIOLOGY:

In the approvable letter the sponsor was requested. The response was adequate.

PHARMACOLOGY/TOXICOLOGY:

During the original review, the remaining deficiency was lack of clarity in the formulation records to support the dosing of the animals in several key studies. The formulation records were submitted, reviewed and were found to be acceptable. Dr. Bailey recommends approval.

CLINICAL PHARMACOLOGY:

During the original review cycle, two studies were performed to evaluate the dosimetry of depreotide. One study (#829-12) was considered pivotal. Another study (#829-10) was not reported fully in the original NDA. The action letter requested the details of this study. Based upon the resubmission (reviewed 6/4/99) and subsequent clarifications (reviewed 7/15/99), the data from study #829-10 are considered to be supportive of the #829-12 study. Of noted, Dr. Sancho's latter review indicates that there are outstanding issues. In verbal discussion, the issue concern is item #4 of the 6/4/99 review page 2. This item notes that 2-5% of the Tc99m is trapped in the thyroid. Dr. Sancho recommends consideration of thyroid blocking for susceptible patients. This issue was discussed with Drs. Loewke and Jones (medical team leader). It was determined that 2-5% of the maximum 20 mCi dose is 0.4 to 1

mCi of Tc99m. This is well within the doses normally given for thyroid scanning with Tc99m and does not require additional study or blocking.

CLINICAL /STATISTICS:

In the approvable letter several deficiencies were listed. These included the lack of sufficient detail to fully characterize the safety database to be used in labeling, the lack of sufficient clarity and consistency to determine which patients should be included in the final evaluable data base and the lack of sufficient clarity to determine the labeled recommendations for the imaging section. The specific deficiencies as stated in the letter are listed in italics.

Dr. Loewke has reviewed the responses to these deficiencies and found them to be acceptable for approval. I agree with her recommendation and have little to add. Her review comprehensively addresses the points and should be read for details. The following is a brief summary of the assessments.

Regarding the safety database characterization: The underlying concern for this deficiency is the change in formulation that occurred during the development of NeoTect. Specifically, the first formulation was not heated; the second formulation was studied in both a heated and unheated method. The original safety database was pooled. The letter requested a separation of the database into the first (investigational formulation), the new formulation unheated, and the new formulation heated. The latter is the one that is proposed for market. Diatide submitted a revised summary of vital signs, laboratory values and adverse events that appropriately separated the formulations. All events were similar. The proposed for market formulation was studied in 647 patients. These data will be used in labeling. The details are summarized in Dr. Loewke's review page 5 -8.

Also, Dr. Loewke's review discusses the occurrence of "clinically significant" changes in hematocrit, hemoglobin and erythrocyte. These were based on the sponsor's definition and noted changes of approximately 0.3 to 9%. In discussion with Dr. Loewke (with the exception of one patient with cancer, peptic ulcer and esophagitis who had a decrease in hematocrit, hemoglobin and blood pressure) none of the patients had clinical evidence of hemolysis or other significant findings. In my opinion, there is not sufficient information to warrant a labeling addition.

Regarding which patients should be included in the final evaluable database: This comment was based upon the need to resolve the number of patients that were protocol violators, the number that did not have histopathology and, or the number that had single pulmonary nodules. Dr. Loewke's review notes that the sponsor's protocol definition of violators does support the sponsor's allocation of patients. However, this definition was based upon a protocol amendment that occurred a few weeks before the enrollment closed. This modification resulted in 40% of the patients with lesions that were biopsied before enrollment. Therefore, the analysis is based on a high percentage of patients with known disease. As Dr. Loewke's review states, this should be identified in the labeling.

The sponsor indicated that the designation of SPN was based upon the screening chest x-ray. The patients were not recoded if the CT scan showed more extensive disease. The data were reanalyzed for those patients who had a SPN on CT. The results were similar to that were reviewed and found to be acceptable during the first review cycle.

Also requested was a subset analysis of SPN patients by the size of the lesion. There were 35/270 (13%) patients (13 in study A, 22 in study B) who had lesions >3 and < 6 cm. The subset analysis suggests that patients with the larger lesions had a higher sensitivity (92 % and 95% vs. 59% and 70% for studies A & B respectively). This difference could occur since an increasing lesion size is associated with malignancy. Likewise, the specificity increased in study A (100% vs. 68%). The specificity could not be calculated in study B because true negatives did not occur in this subset. Overall, however, the number of patients on which these assessments are based is considered too small to support definitive labeling.

SAFETY: A safety update was included in the resubmission and did not demonstrate any substantial differences. These demographics are used in the adverse events section of labeling.

LABELING: As noted above, the sponsor's resubmission included 1) a request to add a section that suggests the superiority of NeoTect with CT or chest x-ray over the use of CT or chest x-ray alone and 2) the revision of the indication to the identification of malignant pulmonary masses. The medical and statistical reviews concluded that neither revision is justified.

Regarding the potential superiority claim: As noted in the preceding section, the number of patients with single pulmonary nodules was in question at the time of the approvable letter and the labeling did not contain any reference to a subset analysis of these patients. Incorporated in the sponsor's resubmission is a request to include an analysis of these patients. The section would include a table that reports the results of a retrospective subset analysis of CT alone, and CT plus NeoTect, and x-ray plus NeoTect. The table would note the apparent improvement of specificity from 7% to 63 or 73% respectively. Similar statements were included in the sponsor's originally proposed labeling. These statements are derived from an analysis that the sponsor identifies as a "pharmacoeconomic study". This "study" is a blinded retrospective analysis of a pooled subset of patients from the two pivotal studies. As such it is not a new study; it is an alternative analysis. Also, it appears to have been

performed after the completion of the primary analysis of the pivotal studies. As per Dr. Mucci's review, the analysis is based on single pulmonary nodules identified on CT during the on site, unblinded analysis of study A and B. Also, a set of blinded readers that were different from those used in the per protocol analysis, evaluated paired CT and NeoTect or paired x-ray and NeoTect images. The sponsor compared these results to CT alone as read by the blinded readers in the per protocol analysis.

As noted in both Dr. Mucci and Loewke's reviews, the sponsor's table comparison to CT can be misinterpreted. The CT abnormality was a requirement for enrollment. The table suggests that NeoTect + x-ray is better than NeoTect + CT. However, CT is known to have advantages over x-ray. As both reviewers noted, a comparison to NeoTect alone suggests that there is better sensitivity but less specificity. Also, the results are dependent upon the background prevalence of disease.

In addition to these concerns, during the first review cycle, it was determined that the combined use of CT and NeoTect depended upon whether the results were both positive. This assessment was derived from the statistical review. This perspective was included in the label to caution of over interpretation of the other combinations.

Therefore, the flaws of the analysis of the SPN subset are its retrospective nature, the comparison of results from several different readers, and the potential to confound the interpretation of the results. Additionally, the analysis is an unplanned assessment that is dependent upon the pooled results. There is not independent substantiation to support a claim of superiority over CT specificity values. This should be further explored in a prospectively designed trial that tests the decision making at the time of the question. Since the net impact of the change in specificity would lead to discharging patients without a biopsy, the confirming data can not be derived in a retrospective sample that is based on a high biopsy positive rate.

Regarding the indication: Diatide requested an indication that NeoTect is a scintigraphic imaging agent indicated to identify malignant pulmonary masses". During the first review cycle this was changed to "NeoTect is a scintigraphic imaging agent indicated to identify somatostatin receptor bearing pulmonary masses in patients who are highly suspect for malignancy and have pulmonary lesions on computed tomography". In the resubmission, Diatide reiterated its request for the indication to identify malignant pulmonary masses. Essentially, Diatide's rationale is that the studies were performed to evaluate the clinical utility in identifying malignancy. While this was the purpose of the studies, as noted in Dr. Loewke's review, somatostatin receptors are found on both normal and abnormal tissues. The study results demonstrate the presence of uptake in non-malignant tissues. Both false positive and false negative results occurred in the trials and the increased positive and negative predict values are depend upon the background prevalence of the study. Therefore, the identification of malignancy (i.e., at the exclusion of other disorders) is not supported sufficiently. However, the patients in whom clinical utility is expected are included in the current labeling statement.

Additionally, Diatide requested that population of intended use was described as "patients with ... pulmonary lesions on computed tomography or chest x-ray". In consideration of this it was determined that all but one patient had a chest x-ray and all except one patient had a CT scan. Therefore, this statement is changed to "computed tomography and chest x-ray".

All other labeling changes in the attached draft are either for clarification or editorial.

ASSESSMENT:

NeoTect is acceptable for approval "as a scintigraphic imaging agent indicated to identify somatostatin receptor bearing pulmonary masses in patients who are highly suspect for malignancy and have pulmonary lesions on computed tomography".

ACTION: Approval

LABELING: As revised and included in the action package

LETTER Inclusions:

A. Pediatric development and exclusivity glossary statements

[Redacted area]

C. Labeling revisions

[Redacted signature] 7/30/99

Patricia Y. Love, M.D.
Director, Division of Medical Imaging and
Radiopharmaceutical Drug Products, HFD-160

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JUL 23 1999

Clinical Review of Response to Approvable Letter

Application Information

NDA # 21012

Sponsor: Diatide, Inc.

Submission Date: January 21, 1999

Clock Date: August 8, 1999

Review Completed: June 7, 1999

Drug Name

Generic: Depreotide trifluoroacetate

Proposed Trade Name: NeoTect™

Chemical Name: Cyclo(L-homocysteinyl-N-methyl-L-phenylalanyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl), (1→1')-sulfide with 3-[(mercaptoacetyl)amino]-L-alanyl-L-lysyl-L-cysteinyl-L-lysineamide

Drug Characterization:

Pharmacologic Category: Radiopharmaceutical

Proposed Indication: Diagnosis of lung tumor

NDA Drug Class: 1 P

Dosage Form and Route of Administration: Intravenous administration of 15-20 mCi Tc99m P829 (50µg)

Related Drugs:

Sandostatin[®], a synthetic somatostatin analogue, is currently used clinically for treating hypersecreting neuroendocrine tumors. Sandostatin[®] is commercially available in the U.S., Europe and Canada.

Octreoscan[®], an indium In-111 labeled synthetic somatostatin analogue, is currently used clinically for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors. (NDA 20314).

Review Team:

Medical: Sally Loewke, M.D.

Biometrics: Tony Mucci, Ph.D.

Biopharm: Alfredo Sancho, Ph.D.

Pharm/Tox: David Bailey, Ph.D.

Microbiology: Paul Stinavage, Ph.D.

Chemistry: Ravi Harapanhalli, Ph.D.

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**APPEARS THIS WAY
ON ORIGINAL**

1.0 CLINICAL ISSUES OUTSTANDING AS CITED IN APPROVABLE LETTER

NDA 21012 was originally submitted for review on June 16, 1998. Depreotide, a Technetium labeled somatostatin analogue, was hypothesized to bind to somatostatin receptors hyperexpressed on the surface of tumor. The two pivotal trials were found to support the following indication: NeoTect™ is a scintigraphic imaging agent indicated as a second line diagnostic (after a positive Tomographic procedure) to detect somatostatin receptor bearing lung tumors in patients who are highly suspect for malignancy. Review of the NDA resulted in an approvable letter issued on December 16, 1998. Outstanding issues requiring resolution were cited for the following disciplines: Clinical, Chemistry Pharm/Tox and Biopharmaceutics. The outstanding clinical issues that required further clarification and or analysis were the following:

A.) The application lacks sufficient detail to fully characterize the safety database to be used in labeling.

- The safety database should be reanalyzed by the subsets of patients who received each formulation. Within each formulation, the data should be analyzed and presented by the different preparation methods (i.e., heating and non-heating).

B.) The application lacks sufficient clarity and consistency to determine which patients should be included in the final evaluable database.

- Within the efficacy database there are inconsistencies in the narrative and line listings on a) the number of patients with protocol violations of biopsies before NeoTect™ (24 in the narrative; 33 patients in the line listings); b) the number of patients with actual solitary pulmonary nodules (65 in the narrative; 42 based upon computed tomography data in the line listings); and c) the number of patients reported as false positive for NeoTect™ (7 in the narrative; 17 in the line listings). Also, an additional 4 patients who were reported as not having biopsy data, had data in the line listings.
- Please clarify and reconcile the database. A reanalysis of the sensitivity, specificity and accuracy should include these patients.
- Also, the analysis of solitary pulmonary nodules was reported for all patients and for the subgroups of patients with lesions of >0 and <3, and those with <6 cm. Please submit an analysis of the subset of patients with lesions of ≥3 and <6 cm.

C.) The application lacks sufficient clarity to determine the labeled recommendations for the imaging section.

- Please clarify in detail which medical imaging procedure was primarily used for the final NeoTect™ image interpretation; (planar, SPECT or both).

This review will address each issue (bold text) and the adequacy of the Sponsor's response in the order as seen above preceded by two review tables: patient disposition data by formulation and demographics for the population receiving the heated/market formulation.

2.0 MATERIAL REVIEWED

The material reviewed was the following:

- Submission with Letter date 1/21/99
- Submission with Letter date 4/21/99
- Submission with Letter Date 5/13/99
- Submission with Letter date 5/21/99

3.0 PATIENT DISPOSITION AND DEMOGRAPHICS

The disposition of patients per formulation and preparation method can be found in Table 1. The heated version of the market formulation is the intended formulation for promotion of this drug. All patients in the pivotal trials received the market/heated formulation. The demographics for the population receiving the market/heated formulation can be found in Table 2.

TABLE 1. Patient Disposition by Formulation Across all Phases of Study

Parameter	Investigational N (%)	Market/Unheated N (%)	Market/Heated N (%)
Total Number of patients enrolled	84	178	649
Number of Patients Administered Study Agent	84 (100)	178 (100)	647(99.6)
Number of Patients Completed Studv	84 (100)	171 (96)	531 (82)

Data Source: Submission Dated 1/21/99, page 050.

TABLE 2. Demographics for the Population Receiving the Market/Heated Formulation

Parameter	Statistic	Market/Heated Formulation, all Phases of Study	Market/Heated Formulation, Phase 3 only	
Total Number of Patients	N	647	270	
Age (yrs)	Mean	58.5	64.5	
	Median	60.0	66.5	
	Std. Err.	0.58	0.70	
	Range	18-86	29-86	
Gender				
Male	N (%)	378 (58)	168 (62)	
Female	N (%)	269 (42)	102 (38)	
Race				
	Caucasian	N (%)	523 (81)	214 (79)
	Black	N (%)	58 (9)	21 (8)
	Other	N (%)	53 (8)	35 (13)
	Missing	N (%)	13 (2)	0
Weight				
	N	632	270	
	Mean	74.2	74.6	
	Median	72.7	72.7	
	Std. Err.	0.68	1.07	
	Range	39-163	41-163	

Data Source: Submission dated 1/21/99, page 052 & 53.

4.0 REVIEW OF RESPONSE TO CLINICAL ISSUE A

A.) The application lacks sufficient detail to fully characterize the safety database to be used in labeling.

- The safety database should be reanalyzed by the subsets of patients who received each formulation. Within each formulation, the data should be analyzed and presented by the different preparation methods (i.e. heating and non-heating).

Adverse Events

Twenty-nine patients receiving the market/heated formulation reported a total of 43 adverse events. None of these events were considered severe in intensity and only 3 events were considered moderate in intensity. The three events rated as moderate were 2 cases of headache and an eye abnormality, which was not further described. The most frequently reported adverse events in the population receiving the market/heated formulation were headache (7/649, 1%), dizziness (5/649, <1%) and nausea (4/649, <1%). The complete listing of adverse events by formulation can be found in Table 3. No significant differences in the adverse event profile were seen between formulations.

TABLE 3. Incidence of Treatment Emergent Adverse Events by Body System and Formulation

Body System/ Preferred Term	Investigational N (%)	Market/ Unheated N (%)	Market/Heated N (%)
Total Number of Patients	84	178	647
Total Number of Injections	85	182	656
Total Number of Patients with any AE	3 (4)	17 (1)	29 (4)
CNS and PNS System	0	3 (2)	13 (2)
Headache	0	2 (1)	7 (1)
Dizziness	0	0	5 (<1)
Cramps, legs	0	0	1 (<1)
Gait Abnormal	0	0	1 (<1)
Hypertonia	0	1 (<1)	0
Hypoaesthesia	0	0	1 (<1)
Gastrointestinal System	1 (1)	7 (4)	7 (1)
Nausea	1 (1)	3 (2)	4 (<1)
Diarrhea	1 (1)	3 (2)	2 (<1)
Vomiting	0	3 (2)	0
Abdominal Pain	0	2 (1)	0
Dyspepsia	1 (1)	0	0
Glossitis	0	0	1 (<1)
Tooth Ache	0	1 (<1)	0
Body As A Whole	0	7 (4)	6 (<1)
Back Pain	0	3 (2)	1 (<1)
Fatigue	0	2 (1)	2 (<1)
Chest Pain	0	0	2 (<1)
Abdomen enlarged	0	1 (<1)	0
Malaise	0	0	1 (<1)
Pain	0	1 (<1)	0
Rigors	0	1 (<1)	0
Syncope	0	1 (<1)	0
Vascular (extracardiac) Disorders	1 (1)	0	3 (<1)
Flushing	0	0	3 (<1)
Vasodilatation	1 (1)	0	0
Respiratory System	0	1 (<1)	2 (<1)
Dyspnea	0	1 (<1)	0
Hemoptysis	0	0	1 (<1)
Pharyngitis	0	0	1 (<1)
Special Senses	0	1 (<1)	2 (<1)
Taste Perversion	0	1 (<1)	2 (<1)
Cardiovascular Disorders	0	1 (<1)	0
Hypertension	0	1 (<1)	0
Endocrine Disorders	0	0	1 (<1)
Endocrine Disorder NOS	0	0	1 (<1)
Musculoskeletal	0	0	1 (<1)
Arthrosis	0	0	1 (<1)
Metabolic and Nutritional Disorders	0	0	1 (<1)
Weight Decrease	0	0	1 (<1)
Platelet, Bleeding/Clotting Disorder	0	1 (<1)	0
Epistaxis	0	1 (<1)	0
Psychiatric Disorder	0	0	1 (<1)
Somnolence	0	0	1 (<1)
Resistance Mechanism Disorder	0	0	1 (<1)
Infection	0	0	1 (<1)
Skin and Appendages	0	1 (<1)	0
Sweating Increased	0	1 (<1)	0
Vision Disorder	0	0	1 (<1)
Eye Abnormality	0	0	1 (<1)
White Cell And RES Disorder	0	0	1 (<1)
Lymphocytosis	0	0	1 (<1)
Application Site Disorder	1 (1)	0	0
Injection site pain	1 (1)	0	0

Data Source: Submission Dated 1/21/99, pages 57-59. Note: Patients reporting a particular adverse event more than once are only counted once within each body system and preferred term. Table includes multiple observations for patients enrolled more than once.

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Vital Sign and Laboratory Data

The Sponsor submitted an analysis of all Phase 2 and 3 study results combined by formulation. The safety data is incomplete because the Phase 1 data is missing from this pooled analysis. The missing data for the market/heated formulation is that from Studies 12 and 13 and consists of a total of 32 patients (21 normals, 5 with hepatic dysfunction, 4 with renal dysfunction and 2 with lung cancer). The safety data for these two studies was, however, submitted in the original NDA and there were no findings that would significantly impact the safety data.

Vital Sign Data:

Of the clinically significant changes reported in vital sign parameters for Phase 2 and 3, no differences between the heated and unheated market formulations were seen. The descriptive statistics (mean and median change from baseline, standard error and range) were similar between the two groups as well (reference Table 6.1, pages 164-167). Of the clinically significant changes reported with the heated formulation, there were no trends identified in any of the parameters monitored. The majority of the patients experiencing a clinically significant change in a single parameter were not found to have associated clinically significant changes in other vital sign parameters at the same time. In my original review of the NDA, it was noted that the cut points the Sponsor chose for a clinically significant change for blood pressure were considered too liberal (Systolic blood pressure +/- 35 mmHg and for diastolic blood pressure +/- 25 mmHg). It was recommended to the Sponsor in a T-con that they should reanalyze this data using the following suggested cutpoints: Systolic blood pressures +/- 25 mmHg and for diastolic blood pressure +/- 15 mmHg. The Sponsor complied with this recommendation and submitted pooled data for Phase 2 and 3 for the market/heated formulation in the submission dated 4/21/99. Review of this data did not show any notable trends. Within the first 30 minutes of monitoring, less than 1% of the population had a clinically significant increase in systolic blood pressure (SBP), \approx 1% had a clinically significant decrease in SBP, \approx 2% had a clinically significant increase in diastolic blood pressure (DBP) and \approx 3% had a clinically significant decrease in DBP. None of these changes were associated with any respiratory or cardiovascular related adverse events.

Laboratory Data:

Descriptive statistics were provided for the laboratory data, as well as, data listings of patients experiencing a clinically significant change in a laboratory parameter compared to baseline per timepoint of collection. The descriptive statistics do not provide any vital information about the patient population studied. The value is even further reduced by the fact that standard deviation information was not provided. Therefore, this review focuses mainly on the data listings (Submission with letter date 4/21/99) describing the clinically significant changes (change resulting in a value outside the normal reference range) in laboratory parameters for the pooled Phase 2 and 3 studies (N=612).

The incidence of clinically significant changes in hematology parameters was reported in the Sponsor's table 5.2 (Submission with Letter date 1/21/99, pg. 099-0102). The greatest incidence of change was seen for hematocrit, hemoglobin and red blood cell (RBC) and lymphocyte count.

A clinically significant drop in Hematocrit ($\leq 37\%M$, $\leq 35\%F$) was found in 34 patients over all timepoints (1 hr, 2-6 hr, or 18-30 hr). Of the 34 patients, 3 had an increase and 31 had a decrease in hematocrit levels. Of the 31 who experienced a drop in hematocrit, nearly half of the patients experienced this solitary drop at the 18-30hr. timepoint. The drop in hematocrit ranged from 0.3 to 9.3 %. Review of a representative sample of these cases did not show any sign of hemolysis as evident by an associated change in total bilirubin, drop in hemoglobin drop in blood pressure or reports of adverse events. In addition, 15 of the 31 patients had an abnormally low baseline value.

A significant drop in hemoglobin (≤ 11.5 g/dL M, ≤ 9.5 g/dL F) was found in 14 patients. Of these 14 patients, 10 patients had a drop in hemoglobin of 1 g/dL or less. The largest drop in hemoglobin was 2.7 g/dL, which occurred in one patient. This patient had a corresponding decrease in hematocrit and drop in blood pressure. No symptoms or adverse events were reported for this patient. This patient was noted to have squamous cell cancer and a history of peptic ulcer disease and esophagitis.

A clinically significant drop in RBC ($\leq 4.0M$, $3.9F \times 10^6/\text{mm}^3$) was found in 42 patients over all timepoints. Of these patients, over half had a decrease in RBC of $0.5 \times 10^6/\text{mm}^3$ or less. Ten of these 42 patients had an abnormal baseline value and 5 had missing baseline values. Only 13 patients had an abnormality identified for more than one timepoint.

A clinically significant change in lymphocyte count was found in 34 patients over all timepoints. Twenty-four patients experienced a clinically significant drop in lymphocyte counts ($<10\%$ or $>60\%$) and 8 patients had a clinically significant rise in lymphocyte counts. Of the 26 patients with a drop in lymphocyte count, 13 patients had an abnormal baseline value and 2 patients had a missing baseline value.

The incidence of clinically significant changes in chemistry parameters was reported in the Sponsor's table 5.3 (Submission with Letter date 1/21/99, pg. 0103-0105). Clinically significant laboratory changes occurred in less than 1% of the population for each parameter at any one timepoint. Review of the line listings revealed that 26 patients who experienced clinically significant changes in either liver or renal function tests. Seventeen of these patients had abnormally high baseline values and four patients did not have a baseline value recorded, therefore, assessment of these changes was limited as to their significance and cause. No significant trends could be identified.

Reviewer's Comment: As seen above, the greatest incidence of clinically significant changes (as defined by the Sponsor) were seen in the following parameters: hematocrit, hemoglobin, lymphocyte, and RBC count. The clinical relevance of these changes cannot be documented. Causality of these changes is unknown. To address this issue, a statement could be made in labeling that states that changes of unknown clinical relevance were found in these particular parameters. The Sponsor has adequately addressed this clinical issue to show the safety of the market/heated formulation. ✓

5.0 REVIEW OF RESPONSE TO CLINICAL ISSUE B

B.) The application lacks sufficient clarity and consistency to determine which patients should be included in the final evaluable database.

- Within the efficacy database there are inconsistencies in the narrative and line listings on a) the number of patients with protocol violations of biopsies before NeoTect™ (24 in the narrative; 33 patients in the line listings); b) the number of patients with actual solitary pulmonary nodules (65 in the narrative; 42 based upon computed tomography data in the line listings); and c) the number of patients reported as false positive for NeoTect™ (7 in the narrative; 17 in the line listings). Also, an additional 4 patients who were reported as not having biopsy data, had data in the line listings.
- Please clarify and reconcile the database. A reanalysis of the sensitivity, specificity and accuracy should include these patients.
- Also, the analysis of solitary pulmonary nodules was reported for all patients and for the subgroups of patients with lesions of >0 and <3 , and those with <6 cm. Please submit an analysis of the subset of patients with lesions of ≥ 3 and <6 cm.

a.) Clarification of patients with protocol violations.

The Sponsor has provided documentation of those patients, which were excluded from the efficacy analysis and the reason for exclusion. Having a biopsy prior to enrollment was not a violation for which a patient was excluded. However, marked discrepancies between text and the data listings for the numbers of violators reported was seen. It was requested that the Sponsor resolve the discrepancy. The Sponsor did not provide this information in the original response, therefore, in a T-con held on April 23, 1999, this information was requested again. In the submission with Letter date of 5/13/99, the Sponsor has addressed this issue. The response identified that an amendment to the protocol was made that allowed for a biopsy to be obtained within six weeks of enrollment. Given this amendment, only those patients falling outside this criterion were considered as violators by the Sponsor. The Sponsor identified six violators for each study (Study 34A and 34B). In the original NDA submission, the Sponsor identified 12 for study A and none for study B. The Sponsor has noted that the identification of 12 violators in the text of Study 34A was a mistake in reporting. Since this type of violation was not considered cause for exclusion, the Sponsor noted that a reanalysis was not needed.

Reviewer's Comment: The amendment to the inclusion criteria, as noted above, was made on 12/8/97. The study was completed on 12/31/97. In addition, the objective of the trial was to study this drug in patients with suspicion of lung cancer. The change in inclusion criteria does not coincide with the objective and was made within 3 weeks of completion of the study, thus bordering on being considered post-hoc by this reviewer.

Referring to my original review dated 12/3/98, approximately 40% of the efficacy evaluable population had known histopathology prior to enrollment. Since this percentage is so large, the labeling must identify that this drug was tested in a population having either known disease or a high suspicion of disease. Despite these issues, however, the Sponsor has responded adequately to the request.

The number of patients with actual solitary pulmonary nodules

The Sponsor used the initial Chest x-ray to delineate a patient with a solitary pulmonary nodule. As noted by this reviewer, there appeared to be CT scans results showing other disease (i.e. adenopathy) present at the time of the SPN diagnosis. Clarification of the total number of patients with a "true" diagnosis of SPN was requested. The Sponsor identified that the original database provided was accurate because the Chest x-ray was considered the criterion for SPN diagnosis. A reanalysis of this data using CT as the definitive diagnosis of SPN was requested in a T-con on April 23, 1999. The results of this analysis were reported in the Submission with the Letter date of 5/13/99. The Sponsor identified 4 patients (1 patient for Study 34A and 3 patients for Study 34B) as having a CT which was interpreted as negative for SPN by the site investigator. The reanalysis excluding these 4 patients did not significantly alter the original efficacy findings.

Reviewer's Comment: As this is a secondary endpoint and the results do not show any clear diagnostic advantage, no labeling claims for this endpoint can be made.

c.)The number of patients reported as false positive for NeoTect™

The Division withdrew this question.

Patients reported as not having biopsy data

In review of the data provided in the original response, discrepancies still existed for three patients (34A-8-06, 34A-10-06 and 34B-5-26). These patients all had a benign histopathology diagnosis made for the biopsy obtained in the data listing provided in the original NDA submission, however, the Sponsor excluded each of these patients for either no histopathology or inadequate histopathology. Further clarification for the above three patients was requested in a T-con with Kris Piper on April 23, 1999. The Sponsor supplied the following explanations (submission with the Letter date of 5/13/99) for the exclusion of these patients:

The Sponsor identified patient 34A-8-06 having the biopsy result of an additional lesion obtained rather than the main presenting lesion. Therefore, since no biopsy of the main presenting lesion existed, this patient was excluded.

Patients 34A-10-06 and 34B-05-26 both had a fine needle aspiration of the main presenting lesion. As per the Sponsor, a "Fine needle aspiration for cytopathology will be considered definitive histopathology assessment if either the results are definitively positive for malignancy or other pathologic process, or if the aspiration is negative and all other diagnostic modalities are not suggestive of malignancy".

Since the histopathology for these two patients was considered as a benign process and other diagnostic modalities were considered suggestive of malignancy, the biopsy was considered inadequate and the patients were excluded from the analysis.

Reviewer's Comment: The Sponsor's explanations show that the decisions were consistent with the stated procedures found within the protocol.

Also, the analysis of solitary pulmonary nodules was reported for all patients and for the subgroups of patients with lesions of >0 and <3, and those with <6 cm. Please submit an analysis of the subset of patients with lesions of ≥ 3 and <6 cm.

Diatide identified that 13 and 22 patients were diagnosed with a SPN between 3 and 6 cm for Study 34A and 34B respectively. Sensitivities and specificities for the individual blinded readers per study for the one-to-one algorithm analysis can be found in the Sponsor's Tables 6.0.8 and 6.0.9. (Submission Letter Date 1/21/99, pages 201-202).

Reviewer's Comment: Given the small numbers within this subset and the variability seen between blinded readers, the interpretation of the drug's diagnostic utility for this subset remains unknown.

6.0 REVIEW OF RESPONSE TO CLINICAL ISSUE C

C.) The application lacks sufficient clarity to determine the labeled recommendations for the imaging section.

- **Please clarify in detail which medical imaging procedure was primarily used for the final NeoTect™ image interpretation; (planar, SPECT or both).**

Diatide responded by identifying that both planar and SPECT imaging of the chest must be performed between 2-4 hours post-NeoTect™ administration. A whole body planar image may be obtained prior to the chest evaluation according to the clinical judgement of the physician, but it would not be necessary for interpretation of the images.

Reviewer's Comment: The label should include that both planar and SPECT imaging of the chest is required.

7.0 CONCLUSIONS:

The Sponsor has adequately addressed the clinical issues cited in the Approvable Letter of 12/16/99.

8.0 RECOMMENDATION: Approval

9.0 LABELING:

A modified version of the adverse event table shown in this review should be used in labeling. Labeling should include the identification of patients enrolled as having known or suspected disease with the percentage of patients with known disease cited. A statement may be included which identifies that changes of unknown clinical relevance were seen in the following laboratory parameters: hematocrit, hemoglobin lymphocyte nad RBC count. The label should include that both planar and SPECT imaging of the chest are required.

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/S/

Sally A. Loewke, M.D. 6/7/99
Medical Reviewer

Dr. Loewke has discussed this review with me and the issues raised in the approvable letter, December 16, 1998, have been addressed by the sponsor. I agree with Dr. Loewke's recommendation of approval.

/S/

6/8/99

A. Eric Jones, M.D.
Clinical Team Leader

I agree with the essence of Dr. Loewke's recommendations. No text is needed for approval. Please see my memo of 7/22/99 for details.

/S/

7/22/99

Patricia Y. Love, M.D.
Division Director

CC: NDA Archive
HFD-160/Division File
HFD-160/J. Moore/Loewke

NDA #21012**Application Information****NDA # 21012****Sponsor: Diatide, Inc.****Submission Date: June 16, 1998****Clock Date: December 16, 1998****Review Completed: December 3, 1998****Drug Name****Generic: Depreotide trifluoroacetate****Proposed Trade Name: NeoTect™****Chemical Name: Cyclo(L-homocysteinyl-N-methyl-L-phenylalanyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl), (1→1')-sulfide with 3-[(mercaptoacetyl)amino]-L-alanyl-L-lysyl-L-cysteinyl-L-lysineamide****Drug Characterization:****Pharmacologic Category: Radiopharmaceutical****Proposed Indication: Diagnosis of lung tumor****NDA Drug Class: 1 P****Dosage Form and Route of Administration: Intravenous administration of 15-20 mCi Tc99m P829 (50µg)****Related Drugs:**

Sandostatin®, a synthetic somatostatin analogue, is currently used clinically for treating hypersecreting neuroendocrine tumors. Sandostatin® is commercially available in the U.S., Europe and Canada.

Octreoscan®, an indium In-111 labeled synthetic somatostatin analogue, is currently used clinically for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors. (NDA 20314).

Review Team:**Medical: Sally Loewke, M.D.****Biometrics: Tony Mucci, Ph.D.****Biopharm: Young-Moon Choi, Ph.D.****Pharm/Tox: David Bailey, Ph.D.****Microbiology: Paul Stinavage, Ph.D.****Chemistry: Ravi Harapanhalli, Ph.D.**

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1.0 Abstract

Technetium Tc99m P829, a somatostatin analog, was studied for its ability to localize tumors which express somatostatin receptors on their surface. This concept was initially studied in animals and in human cell lines to confirm the specific binding of this agent to somatostatin receptors expressed on several tumor cell lines, including various types of lung tumor. Early development in humans focused on patients with neuroendocrine tumors, which have been shown in the literature to commonly express the somatostatin receptor.

During development, both the formulation and dose preparation procedure changed. The new formulation was expected to improve radiochemical purity and the change in dose preparation (from unheated to heated) was expected to make the dose kit more "rugged". The potential impact of these changes on safety and efficacy were not directly studied. Instead, the Sponsor attempted to prove equivalence between the formulations and dose preparations by showing a similar New pharmacokinetic and dynamic studies were performed using the to-be-marketed formulation, however, adequate data to identify the major route of elimination was not obtained.

Dose ranging studies were performed, however, findings did not support any particular dose of activity or peptide. Therefore, dose selection was based on chemistry and imaging characteristics rather than on actual dose ranging study findings.

The pivotal clinical trials focused on localization of lung tumor in part due to the findings in a non-pivotal Phase 3 study that Tc99m P829 performed poorly in the abdomen when compared to Octreoscan. The direction of the pivotal Phase 3 studies allowed for histopathology as the gold standard upon which efficacy was compared. The pivotal studies provided efficacy endpoints which included the sensitivity, specificity and accuracy of the study drug when compared to the histopathology results. These studies, though plagued with inconsistent data, overall, supported a claim of scintigraphic localization of lung tumors bearing somatostatin receptors.

Given the presence of two formulations and two dose preparations, efficacy of this drug was based on the heated version of the market formulation, since this was utilized in the pivotal trials. Tc99m P829 has been found to aid in the detection of somatostatin receptor bearing lung tumors in patients highly suspicious for lung tumor as evidenced by an abnormal radiographic study.

Since the Sponsor did not separate safety data by dose preparation or formulation, safety is based on the pooled database. The pooled database does not suggest any significant safety concern. However, for accurate labeling, a reanalysis by heated, market dose preparation is recommended.

2.0 Material Reviewed

The following NDA volumes were reviewed:

Vol. 1.27-1.83

Submission Date 7/9/1998

Submission Date 7/17/1998: Scatter plots of laboratory safety data for combined Phase 2 and 3 studies.

Submission Date 7/28/1998: Scatter plots for laboratory safety data (Phase 2 and 3).

Submission Date 8/26/1998: Scatter plots for laboratory safety data (Phase 1 and 2).

Submission Date 7/22/1998: Additional Efficacy Text Tables for Pivotal studies.

Submission Date 7/30/1998: Corrected drug formulation development summary

Submission Date 8/13/1998: Text Tables with appropriate references (all Phases).

Submission Date 7/29/1998: Patient listing of type of dose preparation received (Phase 3).

Selected P829 images (CD ROM) from pivotal studies

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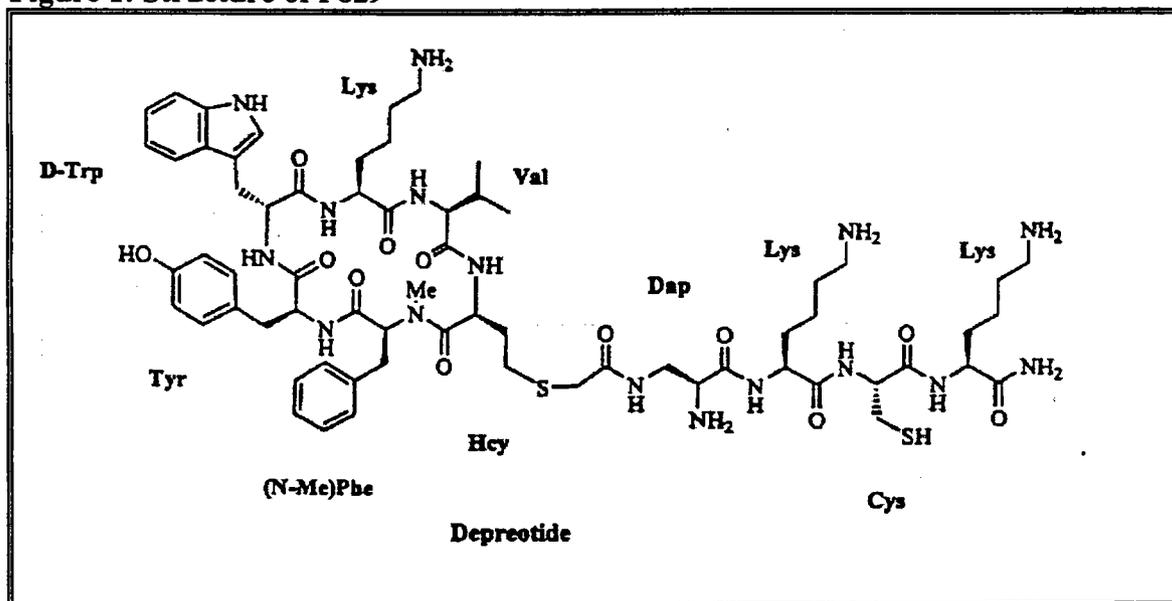
3.0 Chemistry:

3.1 Drug Substance

Chemical Name: Cyclo(L-homocysteinyl-N-methyl-L-phenylalanyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl), (1→1')-sulfide with 3-[(mercaptoacetyl)amino]-L-alanyl-L-lysyl-L-cysteinyl-L-lysynamide.

Depreotide is a synthetic peptide comprised of 10 amino acids. The structure, as seen in the figure, below is composed of a linear tetrapeptide and a cyclic hexapeptide. The cyclic hexapeptide domain contains the amino acid sequence, -Tyr-(D-Trp)-Lys-Val-, which is the bioactive site that binds somatostatin receptors. The linear tetrapeptide contains amino acid sequence, (β-Dap)-Lys-Cys-Lys-, which forms a chelate complex with the radionuclide Technetium Tc99m.

Figure 1: Structure of P829



Depreotide is supplied as a kit preparation which consists of a single dose vial of lyophilized product which is reconstituted with Sodium Pertechnetate Tc99m. In July of 1995, the Sponsor submitted a change in formulation. The changes between the old formulation and the market formulation are summarized in Table 1.

Table 1. Chemical Composition of P829

Component	Market Formulation
Sodium Glucoheptonate Dihydrate	5 mg
Disodium Edetate Dihydrate	100 µg
Sterile Water for Injection	q.s. to 2 ml

The Sponsor used [redacted] methods to study the chemical equivalence between the two formulations. Please see the Chemist's review for further discussion. There was also a [redacted]

[redacted] The latter represents the market preparation. The addition [redacted]

3.2 Manufacturing:

[redacted]

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4.0 Pre-Clinical Pharmacology:

(please see **Pharmacology and Toxicology review**)

The pharmacokinetic properties of Tc 99m P829 followed an open two-compartment model in the rat, rabbit and rhesus monkey. Tc 99m P829 was eliminated from the body with a total clearance of 1-6 mL/min./kg. The major route of elimination was found to be renal.

Single dose toxicity studies were performed in the albino Swiss mouse and albino SPF-NZW rabbit. No deaths were reported in either species up to the highest dose of 1000 μ g peptide/kg in the mice and 600 μ g peptide/kg in the rabbit. Repeat toxicity studies performed in Sprague Dawley rats did not show lethality or treatment-related effects.

Genetic toxicity studies using an Ames bacterial assay indicated that the final formulation of technetium Tc99m P829 is not mutagenic in the bacterial system.

Results of several binding studies with human tumor cell lines indicated that technetium Tc99m P829 binds with high affinity to somatostatin receptors on cell lines derived from human breast, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), lymphoma colon and pancreatic cancers. Technetium Tc99m P829 was found to bind to somatostatin receptor subtypes: SSTR2, SSTR3 and SSTR5.

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5.0 Background Information

5.1 Indication: Technetium Tc99m Depreotide is indicated for the scintigraphic imaging of malignant tumors in the lung.

5.2 Related NDAs:

NDA 20314: indium In-111 pentetrotide, Octreoscan®

5.3 Foreign Marketing

Neotect™ is not marketed in any country.

5.4 Directions For Use

Tc99m Depreotide is formed from the reconstitution of the drug product in Kit preparation with Sodium Pertechnetate Tc99m injection obtained from a commercially available Mo99/Tc99m generator and incubating the solution in a boiling water bath for 10 minutes. The solution is allowed to cool to room temperature and is analyzed for radiochemical purity [redacted] Tc99m P829us injected intravenously within 5 hours of reconstitution. The dose to be administered is 15-20mCi of Tc99m and up to 50µg of P829 peptide.

5.5 Human Pharmacokinetics and Pharmacodynamics:

(Please see BioPharm review)

Clinical studies were performed in humans using the original and to-be-market formulation. Pharmacokinetic data was based on the radioactivity administered rather than the P829 peptide. Studies in normal volunteers and in patients demonstrated that the tracer follows a three-compartment model with a distribution half-life of less than five minutes and a terminal half-life of about 20 hours. Total clearance averaged 1.5 to 4 mL/min/kg. Renal clearance averaged 0.2 to 0.4 mL/min/kg. Six to 17% of the injected dose of radioactivity appeared in the urine at four hours after injection. No other route of elimination was investigated by the Sponsor. Information regarding the metabolism, or lack thereof, has not been adequately established. It is important to note that since the major route of elimination in animals was found to be renal, this data cannot be used to support the limited elimination data collected in humans.

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5.6 Introduction to the Reader:

All studies submitted were reviewed and presented regardless of formulation and dose preparation. Those studies using the proposed for market formulation and its heated preparation method are presented in the key sections of the NDA review. Those studies using earlier formulations or dose preparations are presented at the end of the review.

During the development of Depreotide, two different formulations and two dose preparation methods were used in the clinical studies. The first formulation was referred to as the investigational formulation and the second was the proposed for market formulation. The two different dose preparations, heated and unheated, were used with both formulations. The proposed market formulation will be heated. A table identifying the total number of patients receiving each formulation and dose preparation follows below.

At the time of this writing, whether the formulations and associated preparations method are completely bioequivalent in their pharmacokinetic and pharmacodynamic parameters is not clear. Therefore, the major NDA conclusions are based on the proposed for market formulation, heated preparation.

A summary Table of all phase 1 and 2 studies follows. This table provides concise information of formulation used, objectives, sample size and results. Overall, there were 2 of the 4 Phase 1 studies carried out using the heated, market formulation (P829-12 and 13). These two studies provide information on the pharmacokinetic and biodistribution of the study agent.

Of the 5 Phase 2 studies, only one study utilized the heated version of the market formulation (p829-30II/a). This study was performed in 13 patients with lung tumor and offers support for the pivotal trials. No dose ranging study was performed using the heated, market formulation. Two dose ranging studies were performed, one using the heated investigational formulation (P829- 20) and one using the unheated market formulation (P829-23). Neither study supported the use of any one specific activity or peptide dose.

Two pivotal studies (P829-34A & B) serve as the major support for this NDA. Three other non-pivotal Phase 3 studies were performed, two in patients with neuroendocrine tumors and one in patients with malignant melanoma. The information provided by these trials offers support for a somatostatin receptor claim as part of the indication.

Following the summary table, the reviews of the relevant studies P829-12, 13, 30II/a, 30A & B and 32 are presented. Following this, the review of the pivotal trial design and the individual pivotal reviews will be presented. This will be followed by the overview of safety and efficacy and the final recommendation.

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Of the 909 patients exposed to study drug, 54% were male and 46% were female. The mean age was 56.7 years with a range of 18 to 87 years. The number of patients studied per Phase of study, formulation and dose preparation can be found in the table below.

Breakdown of the Population by Formulation and Dose Preparation Administered.

	INVESTIGATIONAL FORMULATION		TO-BE-MARKETED FORMULATION		TOTALS
		HEATED		HEATED	
Phase 1					69
Study 10			17		
Study 11			20		
Study 12				23	
Study 13				9	
Phase 2					255
Study 00		23			
Study 20		43			
Study 22	19		34	77	
Study 23			46		
Study 30IIa				13	
Phase 3					586
Study 30A			18	98	
Study 30B			36	99	
Study 32				65	
Study 34A				128	
Study 34B				142	
TOTALS	19	66	171	654	910*

*Several Patients received multiple doses and each injection was counted as a new patient. This total does not match the Sponsor's findings and it is not clear where the discrepancy lies.

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6.1 Brief Summary of Phase 1 and 2 Studies Summary Table of Phase 1 and 2 Studies.

STUDY	FORMULATION	OBJECTIVE	POPULATION	DOSE	SPONSOR'S RESULTS	REVIEWER'S CONCLUSION
P829-10 Phase 1	Market Lots 9509M01A & 9509M01B	Safety Biodistribution Clearance Dosimetry	17 Healthy Volunteers	8.3-10.8mCi 35-50µg	Rapid blood clearance Long terminal half-life of 17.9hrs. Urinary Excretion 5.3-7.7% No safety concerns	Radiation dosimetry and PK for parent compound not adequately addressed. Limited urinary excretion. Major route of excretion not studied. No significant safety concerns
P829-11 Phase 1	Market Lot: not specified	Safety Imaging patterns	20 Healthy Volunteers	8.7-21.1mCi	No efficacy Results-images to be read as part of a later study (829-30) No safety concerns	Image reads for efficacy analysis should be summarized and reported by the Sponsor. No significant safety concerns identified.
P829-12 Phase 1	Market Lots 9609B02F & 9609B02G	PK Radiation dosimetry Immunogenicity Renal/hepatic dysfunction.	12 Healthy Volunteers 4 Renally Impaired Patients 5 Hepatically impaired patients 2 Lung cancer patients	8.2-15.3 mCi Actual peptide doses were not reported, however 50 µg was planned	Rapid blood clearance Long terminal Half-life of 19.8 hrs. Significant gender effect on clearance identified. No difference in Kinetics for renal and hepatic and lung cancer patients Highest activities seen in liver and kidney No safety concerns	Route of elimination and identification of the presence of parent drug metabolism has not been addressed. Meaning of gender affect seen on clearance is not known. No significant safety concerns. Limited sample size for subpopulation studied (renally and hepatically impaired and lung cancer patients). Also extent of disease was marginal in some cases. Therefore no generalized statements of the safety in these subgroups can be made.
P829-13 Phase 1	Market Lot 9609B02G	P829 effect on normal physiologic response to glucose challenge Immunogenicity	9 Healthy Volunteers	Unlabeled drug was used Actual peptide doses were not reported but 50 µg was planned to be administered	P829 does not alter physiological response to a glucose challenge P829 did not lead to the generation of P829 specific antibodies.	No abnormal trend in glucose serum levels seen post-P829 administration in healthy volunteers. No significant safety concerns identified.
P829-00 Phase 2	Investigational Lot 94183-13/28	Feasibility of imaging somatostatin receptor bearing tumors; comparison with In-111 pentetreotide Safety - Adverse events only	21 patients with melanoma 2 patients with pituitary tumors	9.5-20.0 mCi 40-87 µg	Comparison of Tc99m P829 results with clinical truth 87.5 % sensitivity 83% specificity 86.4% accuracy No safety concerns	Did not utilize to-be-marketed formulation, therefore findings are not pertinent to the overall efficacy or safety of the NDA.
P829-20 Phase 2	Investigational Lot: Not specified	Dose ranging Detection of neuroendocrine tumors and lymphoma Safety	43 patients with neuroendocrine tumors and lymphoma (6 patients had non-small cell lung cancer)	7.2-19.4 mCi No actual peptide dose ranges provided.	No efficacy evaluation Single injection at all dose levels was well tolerated.	A change in formulation was made. No efficacy analyses were performed No significant safety trends identified Since the to-be-marketed formulation was not used, no pertinent information was obtained.

STUDY	FORMULATION	OBJECTIVE	POPULATION	DOSE	SPONSOR'S RESULTS	REVIEWER'S CONCLUSION
P829-22 Phase 2B	Investigational and Market Formulations Lot 9509M02A, 9509B01B, 9609B02E, 9509B01D, 9509M01A	Detection and localization of somatostatin receptor expressing tumors Safety	130 patients 19- investigational formulation (unheated) 77 market formulation (heated) 34 market formulation (unheated). 28/131 patients had lung cancer	6.5-19.2 mCi 10.1-50.0 µg (Amount of peptide dose was not standardized)	Technetium Tc-99m P829 administered as a single intravenous injection to patients with a clinical diagnosis of cancer was safe and well tolerated. Technetium Tc-99m P829 can detect somatostatin receptor-expressing tumors and in particular has the ability to detect cancer of the lung.	The design of the study not ideal for the objectives of this trial. Efficacy, when reviewed in the context of diagnosis of lung tumor, does offer some information to show that this agent does localize in lung tumor. Efficacy bases on Lung tumor type was not performed. Efficacy should be re-assessed per dose preparation method. Safety conclusions cannot be made due to the existence of two variables, namely formulation changes and dose preparation changes, which were not addressed by the Sponsor.
P829-23	Market Formulation Lot 9509M01A & B, 9509B01B & D	Dose Ranging (peptide and radioactivity) Detection and localization of Tc-99m P829 in somatostatin receptor expressing tumors	46 patients with tumors suspected of expressing somatostatin receptors: 4/46 (8.7%) small cell lung cancer	6.84-21.7mCi Actual peptide doses not reported. Protocol planned for the administration of 10, 20 and 50µg of P829 peptide.	No one activity or peptide dose clinically superior to the other combinations tested. However, the Sponsor chose the 20mCi and 50µg doses as the optimal dose for future study.	Rationale for selection of 20 mCi is sound. Rationale for selection of 50 µg peptide dose is not understood. Impact of the use of the non-heated dose preparation is not known. No apparent safety trends identified in this study utilizing the unheated dose preparation.
P829-301A	Market Formulation Lot 9609B02B	Detection of primary and metastatic non-small cell lung cancer. Safety- assessed by adverse events only.	13 patients 6 Squamous cell 5 Adenocarcinoma 1 Large cell 1 No biopsy obtained	16.0-22.0 mCi Actual peptide dose administered was not specified Planned peptide dose was 50µg	Patient based agreement rate of 100% was reported between Tc-99m P829 and Tc-99m P829 and histopathology. No adverse events were reported.	No lesion site specific rate of agreement between Tc-99m P829 and histology was performed. Study supports further investigation into the ability of Tc-99m P829 to detect lung cancer. Inadequate safety assessment performed.

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Phase 1

Of the 4 Phase 1 studies, all utilized the market formulation, but only studies 12 and 13 utilized the heated dose preparation. Since the pivotal studies utilized the heated dose preparation of the market formulation, only the data from study 12 and 13 are relevant. Study 12 failed to identify the major route of elimination of the drug product. Low renal clearance was identified indicating an excretory route other than renal. A long terminal half-life of 19.8 hours was identified with low plasma protein binding (12%). A statistically significant gender effect on clearance rates was identified. This effect was not adequately assessed by the Sponsor. No specific safety trends in either the vital sign or laboratory data were identified. Safety was not assessed by gender in the individual studies however. No comments regarding the safety of this drug in renally impaired, hepatically impaired or cancer patients can be made.

Study 13 was performed to assess the effect of P829 on the physiologic response to a glucose load. This study used Octreotide, a therapeutic drug which is a somatostatin analog as a comparator. Findings did not suggest any direct effect of unlabeled P829 peptide (50µg) on the post-GTT glucose values. There was no comparison with the approved diagnostic somatostatin analog, Octreoscan, which utilizes a peptide dose (10 µg) which is markedly lower than P829. Safety assessment were confounded by the administration of Octreoscan and Glucola.

Phase 2

One (30/IIa) of the 5 Phase 2 studies utilized the heated market formulation and therefore is relevant. Study P829-23 utilized the [redacted] dose preparation of the market formulation. The impact of the heating process is not adequately addressed, therefore the influence it may have on the efficacy and safety is not known. Study P829-22 utilized both formulations and both dose preparations, however, the Sponsor did not breakdown the results by dose preparation.

Study P829-23 looked at dose ranging in a wide variety of tumor types. Only 4 of the 46 patients enrolled had lung cancer. The findings of this study did not support any one particular activity or peptide dose. The Sponsor made a selection for the optimal dose of 20 mCi and 50 µg of peptide. The rationale for the activity dose is sound, however, the rationale for the peptide dose is not clear. No dose ranging study was performed using the heated, market formulation.

Study P829-30/IIa is the only study that could directly provide supportive information for the pivotal studies. This study was done specifically to look at the utility of Tc99m P829 in the detection of non-small cell lung cancer. The formulation used and dose preparation mimic that which was used in the pivotal trials. This study does provide minimal support (sample size of 12) for the further investigation into the use of this drug in detecting lung cancer. Unfortunately, the safety assessment was very limited (adverse event reporting only), therefore, the supportive safety information available for the use of the heated market formulation is also limited.

PHASE 1
STUDY P829-12