

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 021012**

**STATISTICAL REVIEW(S)**

Addendum to Statistical Review of NDA# 21012

Sponsor: Diatide

Drug: NeoTect

Original NDA Statistical Review Date: Nov 23 1998

NDA Supplement Document Date: June 18 1999

Medical Officer: Sally Loewke, M.D.

Statistical Reviewer: A G Mucci, Ph. D.

CSO: James Moore

*Overview*

Diatide's June 1999 submission consists of a revised Package Insert for NeoTect. The June 1999 revisions to the Clinical Studies section of the Package Insert which are of statistical relevance are:

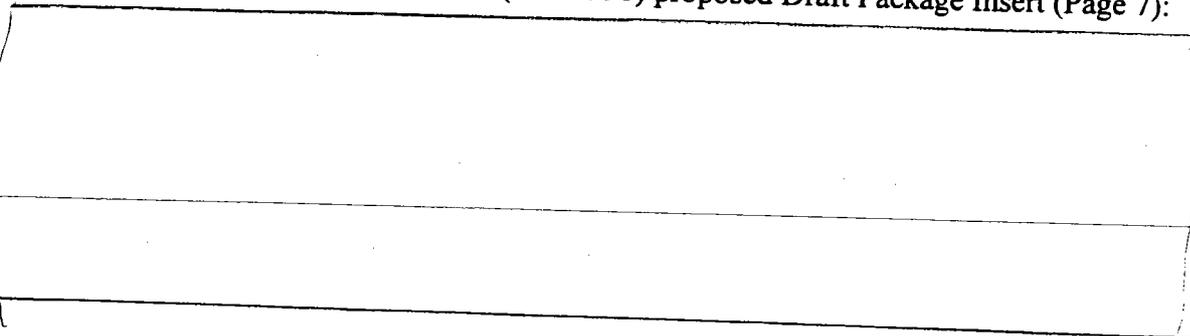
(1): The deletion of a paragraph from page 7 of most recent (Dec 1999) FDA proposed Draft Package Insert.

(2): The re-instatement of a statistical table from an earlier (June 1998) Diatide proposed Draft Package Insert.

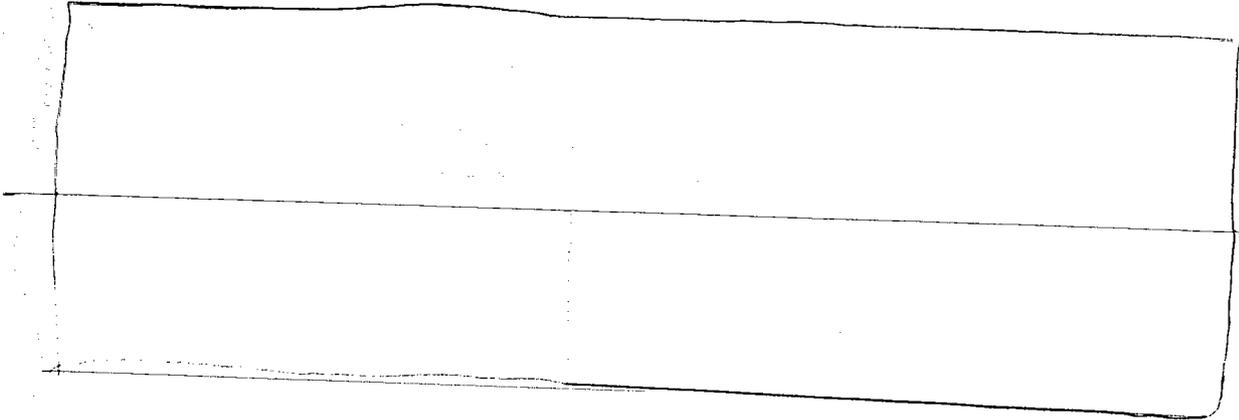
(1) and (2) are related, in that the re-instatement(2) is most likely intended to provide results analogous to, but stronger than, those provided in the deletion(1):

Details on Deletion(1):

The sponsor's recent (June 1999) Draft Package Insert deletes the following paragraph from the Clinical section of the FDA (Dec 1998) proposed Draft Package Insert (Page 7):

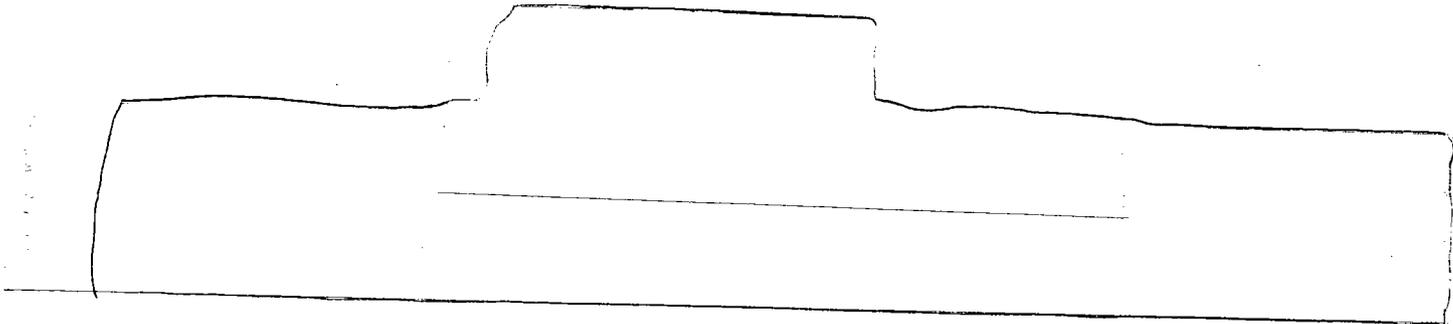


The Statistical Reviewer's slightly modified version of this paragraph is presented directly below. This modification is identical in intent with the italicized paragraph above, and is provided here for more precise characterization of the therein cited retrospective scenario:



Details on Reinstatement(2):

A retrospective study was conducted by the Sponsor on the subpopulation of patients whose Xrays/Cscans presented Solitary Pulmonary Nodules (SPN), as determined by on-site investigators. *This retrospective study followed upon completion of Safety and Efficacy analyses of Pivotal Trials P829-34A and P829-34B, (see NDA21012, Vol#1, page 4) and consisted of new blinded reads in which three new readers were engaged to independently view Neotect Images in conjunction with CT Scan and another three new readers were engaged to independently read NeoTect Images in conjunction with Xray. The CT scans and Xrays were instrumental primarily in SPN localization, but this localization was the responsibility of the new readers and was not provided to them through any annotations on the images. The Sponsor had earlier provided a table with the results of this retrospective study in the June 1998 Draft Insert Package. The FDA deleted this table from its Dec 1999 Draft Insert Package, and the Sponsor reinstated it in June 1999. The Sponsor's reinstated table( Table(8)) is found on Page 8 of the June 1999 Draft Insert Package. This table is duplicated directly below:*  
The statistics are calculated relative to a majority read.



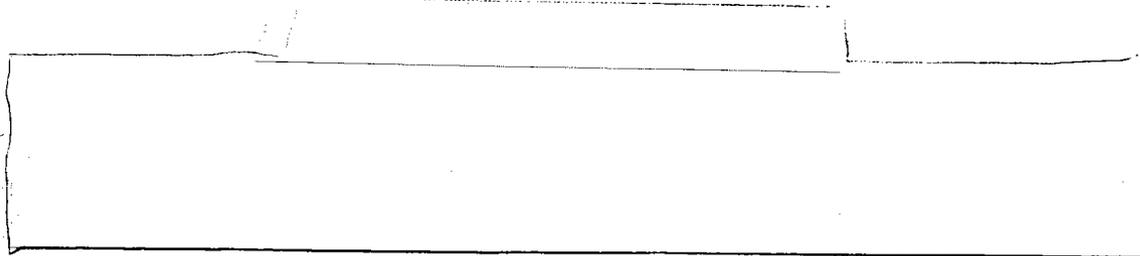
*Presumably, these statistics are intended to replace and improve the import of the deleted paragraph(1) above.*

*Before entering into a critical analysis of these several deletions and replacements, the Statistical Reviewer would like to present a modified version of table(8). The Reviewer's version of table(8) differs from the Sponsor's in the replacement of the CT Scan Alone data with NeoTect Alone data, and in the addition of confidence intervals, along with supporting sample size information. The replacement of the CT Scan Alone statistics with NeoTect Alone statistics is justified here by an appeal to caution – abnormalities on the on-site CT Reads provided the principal inclusion criterion for the pivotal trials, consequently Sensitivities would be very high and Specificities would be very low, and therefore, for instance, the increased Specificities for paired CT/NeoTect vis a vis CT Scan Alone are exist almost by default, and should not carry much weight, whereas no expectations exist a priori as to the value of NeoTect Reads Alone, and the inclusion of statistics on such reads could serve to temper any inclination to use NeoTect as a stand-alone. (Note: The CT Statistics in the table above came from Pivotal Trial Blinded Majority Reads, but these reads revealed negligible differences from the inclusionary on-site reads.) Finally, a predictive value table is appended; this table is added primarily to draw attention to the critical role of prevalence.*


A table of Predictive Values is presented below. This table is derived from Sensitivities and Specificities determined from NeoTect Alone Blinded Reads for the entire patient population (not just SPN patients). This extension from SPN patients to all patients produces only negligible differences in Predictive Values since Sensitivities and Specificities derived from NeoTect Alone Reads for the entire patient population do not differ significantly from the corresponding Sensitivities and Specificities derived from NeoTect Alone Reads for the more limited SPN patient population:

NeoTect Reads - All Patients: Sensitivity = .71 Specificity = .83 Prevalence = .81

NeoTect Reads - SPN Patients: Sensitivity = .65 Specificity = .85 Prevalence = .79



*Critique/Recommendations regarding the Sponsor's Deletions(1) and Additions(2)*

*The Statistical Reviewer's most serious objections to the inclusion of the Sponsor's Table(8) in Labeling is that the CT Alone Reads provide statistics biased by the fact that positive CT served as an Inclusion Criterion, and, further, that these reads were performed by different readers than those who performed the paired reads. The Reviewer continues to find advantages in his alternative, Table(8)', namely: for Sensitivities and Negative Predictive Values, the tables (8)' and (8)" highlight the inadequacies of NeoTect as a stand-alone.*

*In any event, none of the Specificities or Negative Predictive Values, - neither those derived from Neotect Alone, nor those derived from paired reads, - should be interpreted as large enough to override the need for biopsy in patients so strongly suspicious of malignancy as are those who were included in these trials.*

/S/

7-22-99

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HFD-715/E Nevius/M Welch/M Sobhan/A Mucci

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STATISTICAL REVIEW AND EVALUATION

NOV 23 1998

NDA# 21012

SPONSOR: Diatide DRUG: Depreotide ( Technetium Tc 99m P829)

DRUG CLASS: 1P

INDICATION: Scintigraphic Imaging of the Lung

DOCUMENT DATE: July 23 1998

PDUFA DATE: Dec 16 1998

MEDICAL OFFICER : Sally Loewke, M.D. CSO: Catalina Ferre-Hockensmith  
STATISTICAL REVIEWER: A G Mucci, Ph.D.

Pivotal Protocols: P829-34A P829-34B

Protocol Title: *A Multicenter Study Evaluating the Safety and Efficacy of Technetium Tc 99m P829 ( Depreotide ) for the Detection and Localization of Cancer in the Lung.*

**Trial Objectives:**

- (1): To evaluate the Safety of Technetium Tc 99m P829 in patients presenting with suspicion of Cancer in the Lung.*
- (2): To evaluate the Efficacy (Accuracy) of Technetium Tc 99m P829 for the Detection and Localization of Primary and Metastatic sites ( Hilar and Mediastinal lymph nodes ) in patients with suspicion of Cancer in the Lung.*

**Proposed Indication:** *Technetium Tc 99m Depreotide is indicated for Scintigraphic Imaging of Malignant tumors of the Lung.*

**Contents of Statistical Review**

- (I): Statistical Reviewer's Principal Conclusions*
- (II): Overview of Clinical Trial Protocols and Principal Results for Combined Trials*
- (III): Detailed Analysis of Protocols*
- (IV): Critical Comments on Trial Design and Its Implementation*
- (V): Detailed Tables and Statistical Analyses*
- (VI): Statistical Reviewer's Final Critique/Comments*

*(I): Statistical Reviewer's Principal Conclusions*

*These Clinical Trials provide Sensitivities, Specificities, and Accuracies of Depreotide Image Reads with respect to Histopathology for subjects with Lung Abnormalities initially detected on CT Scans/Xrays. The restriction of Depreotide Efficacy Analyses to such subjects, along with the Sponsor's explicitly stated rationale that, for such subjects, Depreotide Images could provide differential diagnoses obviating the need for biopsies, points towards Specificity as the critical Efficacy Endpoint. The trial results do indicate that Depreotide provides reasonably good Specificities, but the numbers are not so strong as to modify decisions to biopsy. Moreover, the population of healthy patients is too small to support definitive conclusions regarding Specificities. The only unambiguous result of these trials is the very strong evidence provided for malignancy when disease prevalences are high, and when both Blinded CT Scan Reads and Blinded Depreotide Image Reads are positive. This result would favor biopsy when positive Cscan alone might not appear decisive. However, there is no real evidence that negative Depreotide Images are trustworthy indicators of benign health status when CT Scans and prevalence rates both suggest otherwise.*

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(II): *Statistical Reviewer's Overview of the Pivotal Trial Protocols*

Study Rationale/Objectives/Proposed Indications/Endpoints:

Depreotide Imaging is intended as a non-invasive method for the differential detection of malignancy in abnormalities originally detected anatomically on CT Scans/Xrays. Efficacy will be evaluated through comparison of Depreotide Reads with Histopathology Results for one specific biopsied abnormality per patient. This abnormality is designated as the Main Presenting Lesion.

The proposed Indication is: *Technetium Tc 99m Depreotide is indicated for Scintigraphic Imaging of malignant tumors of the lung.*

The proposed Endpoints are: *Sensitivity/Specificity/Diagnostic Accuracy*

The sponsor submitted results and analyses for two pivotal trials - P829-34A and P829-34B. These protocols were identical, and consisted essentially of the following elements:

(A): An Inclusionary Unblinded CT Scan and Xray, at least one of which is suggestive of lung tumor.

(B): A Biopsy of a specific abnormality in a specific lung region, typically directed by the Unblinded CT Scan/Xray results. The Histopathology result for the specified abnormality, which is designated as the Main Presenting Lesion, provides the Standard of Truth for these trials.

(C): Depreotide Imaging of the lung.

(D): Three Independent Blinded Depreotide Image Reads and Three Independent Blinded CT Scan Reads ( different readers for each Modality and each pivotal trial)

(E): Standard Efficacy evaluations, - Sensitivities, Specificities, and Accuracies - for the various Blinded Reads, where all Primary Efficacy evaluations were conducted with respect to criteria of Concordance/Discordance of Blinded Read Results with Histopathology Results exclusively for the Main Presenting Lesion. Two criteria were used for Concordance:

The '1-1' Criterion - Image and Histopathology must agree both as to Location and Diagnosis of the Main Presenting Lesion.

The Adjacent Criterion - Image and Histopathology must agree as to Diagnosis, but the Image needs only locate the Lesion 'near' ( defined later, in Section(IV) below ) the histopathologically specified location for the Main Presenting Lesion.

P829-34A enrolled 128 patients, of whom 112 were evaluable  
P829-34B enrolled 142 patients, of whom 114 were evaluable

The principal cause of non-evaluability, affecting 14 patients in P829-34A and 26 patients in P829-34, was the absence of a histopathological evaluation. Since all Efficacy evaluations require histopathology, all analyses were restricted to evaluables only.

Note: CT Scans will be denoted Cscans in all further discussions below.

*Principal Clinical Trial Results: ( Reviewer's Tables)*

The principal Depreotide Image and Cscan Sensitivity, Specificity and Diagnostic Accuracy Results for trials P829-34A and P829-34B combined (226 subjects) are presented in Table(A) directly below. It should be understood that Cscans are not intended as a Comparator in these trials, and therefore Cscan performance measures are included strictly for the purpose of highlighting their possible differences from Depreotide Image Read performance measures, or, for the purpose of signalling potential performance "synergisms" when Depreotide Images and Cscans are used together. All of these diagnostic measures are calculated for Blinded reads, and are further calculated as either 'Worst Case' or 'Best Case' Majority Reads, which are defined as follows:

(1): For the Depreotide Images: If any of the three Blinded Reads are unspecified for any of the regions involved in establishing Concordance/Discordance with Histopathology, then these regions are assigned values discordant with Histopathology.

(2): For the Cscans: If any of the three Blinded reads are unspecified for any of the regions involved in establishing Concordance/Discordance with Histopathology, then these regions are assigned values concordant with Histopathology.

(3): Subsequent to the assignments specified under (1) and (2), the three Blinded Depreotide Reads and the three Cscan Reads are each reduced to single Majority Reads.

For completeness, a table of Positive and Negative Predictive Values is included as Table(B) below.

Note that Table(A) lists values for diagnostic measures for both the 1-1 Analysis and the Adjacent Analysis, while Table(B) restricts attention to the 1-1 Analysis.

The Statistical Reviewer's comments follow the tables.

More detailed tables of results will be presented in Section(V).

Table(A)  
 ( Based on Combined Evaluables = 226 Patients with Healthy=184 and Diseased=42)

	SENS(I)	SENS(C)	SPEC(I)	SPEC(C)	ACC(I)	ACC(C)
1-1 ANALYSIS	.71	.93	.83	.26	.73	.81
ADJ ANALYSIS	.84	.96	.60	.05	.73	.79

SENS(I)/SPEC(I)/ACC(I)= Sensitivity/Specificity/Accuracy for Majority 'Worst Case' Blind Read of Depreotide Images  
 SENS(C)/SPEC(C)/ACC(C)=Sensitivity/Specificity/Accuracy for Majority 'Best Case' Blind Read of Cscan Images

Table(B)  
 ( Pos Pred Val and Neg Pred Value of Depreotide Images as Functions of Prevalence)

PREVALENCE	POS PRED VAL	NEG PRED VAL
PR= .37	.67	.82
PR= .50	.82	.74
PR= .67	.90	.60
PR= .80	.95	.43

The entries above were calculated for the 1-1 Algorithm  
 The actual Prevalence for the combined Trials was Pr=.81.  
 The PPV and NPV values listed in the table for the various choices of PR were calculated in two ways:  
 Theoretically, using the Sensitivity and Specificity values from Table(A)  
 Empirically, through prevalence based random resampling(bootstrapping) from the 226 subjects

## Comments on the Tables

*Table(A): The only clear advantage for Depreotide Imaging over Cscans lies with Specificities. This is to be expected, since Cscan Abnormalities constituted the principal category for trial Inclusion. In fact, the trial rationale specifies clearly that the purported value of Depreotide Imaging lies in the possibilities it might offer in further differentiating Cscan anatomical findings into benign or malignant. The Accuracies achieved by Depreotide Images are unexceptional, given the disease prevalence rate for the combined trials: PR=.81. In fact, given the context imposed by the trial, namely that Cscans and or Xrays indicated an anatomical abnormality, and given this high prevalence rate, an unblinded investigator presented with the Cscan information and the prevalence rate, could, by simply declaring 'malignancy' for the Cscan finding, and without recourse to Depreotide Reads, achieve Accuracies of .80. This possibility is mentioned here not for the purpose of downplaying the value of Depreotide Images, but rather to indicate the irrelevance of Diagnostic Accuracy as an Efficacy Endpoint in these trials.*

*Table(B): Again, the trial rationale would seem to implicate Negative Predictive values as significant for the evaluation of the utility of Depreotide Images. In order to evaluate NPV objectively, that is, under circumstances involving different prevalences, two approaches were taken. First, the Sensitivities and Specificities from Table(A) were accepted as 'stable', that is, valid in general circumstances, and then PPV and NPV were calculated theoretically. Alternatively, the data from this trial was subjected to random subsampling to yield random subclasses of subjects who would satisfy the several prevalence criteria - .37, .50, .67, .80 - and PPV, NPV, Specificity, and Sensitivity were directly calculated for these subclasses. In all such cases the Sensitivities and Specificities listed in Table(A) prevailed, and the PPV and NPV values matched the theoretical values. Consequently, the particular PPV values obtained, and, for the special intentions of these trials, the particular NPV values obtained, possess some measure of "replicability". The significant question then becomes: is the NPV value large enough to present strong evidence that Depreotide Images provide a differential advantage in diagnosis, in the sense that negative Depreotide Reads could modify a diagnosis, one of whose components is a positive Cscan? This doesn't appear to be so when Prevalences are high, as is the case in these trials.*

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*(III): A More Detailed Treatment of Study Rationale/Study Objectives/Pivotal Study Protocols*

There were two Pivotal Study Protocols - P829-34A and P829-34B. These Protocols had identical rationales, objectives, and designs, while the actual Clinical Trials involved separate and independent groups of patients, investigators and image readers. The protocol synopsis below will therefore apply simultaneously to both Pivotal Study protocols. Differences in protocol implementation per clinical trial - number of patients, disposition of patients with respect to inclusion criteria, etc, - will be addressed wherever appropriate.

*Protocol Title: A Multicenter Study Evaluating the Safety and Efficacy of Technetium Tc 99m P829 for the Detection and Localization of Cancer in the Lung.*

*Rationale for Study(Volume#1, Section 3A):*

*Xray/CT/MRI provide only anatomical information - presence and location - of abnormalities suspicious of lung cancer; the further differentiation of these abnormalities into benign and malignant tumors, and the accurate staging of associated metastases, currently require invasive procedures. Consequently, a medical need exists for a non-invasive method for the differential detection of malignant tumors of the lung. Somatostatin receptors (SSTR's) are sometimes hyper-expressed on malignant tumors, therefore an Imaging Agent consisting of an SSTR-binding peptide and a radioisotope could potentially provide a non-invasive means of characterizing lung lesions as malignant/benign, thereby avoiding the morbidity and mortality associated with biopsy and exploratory surgery. Technetium Tc 99m Depreotide, which consists of the SSTR binding peptide Depreotide (P829) and the radioisotope Technetium Tc 99m, is proposed as such an Imaging Agent.*

*Study Objectives ( Protocol P829-34 Dec 8 1997 Volume 119)*

*(1): To evaluate the safety of Technetium Tc 99m P829 in patients presenting with suspicion of cancer in the lung.*

*(2): To evaluate the Efficacy (Diagnostic Accuracy) of Technetium Tc 99m P829 for the detection and localization of primary and metastatic sites in patients with suspicion of cancer in the lung. Efficacy will be assessed through comparison of Technetium Tc 99m P829 scan results with histopathology.*

*Proposed " Indications and Usage" Statement (Volume 83 pp 78-80)*

*Technetium Tc 99m Depreotide is indicated for Scintigraphic Imaging of malignant tumors of the lung.*

Clinical Design:

Multicenter - 13 Centers for P829-34A; 16 Centers for P829-34B

Sample Size - P829-34A: 128 Enrolled, 112 Evaluable; P829-34B: 142 Enrolled, 114 Evaluable

Principal Inclusion/Evaluability Criteria:

*Patients present with suspicion of cancer in the lung.*

*Patients must have a chest Xray and a CT Scan of the chest area within six weeks of Enrollment.*

*Patients are to be scheduled for a procedure in which a specimen for histopathological confirmation will be obtained within six weeks of Enrollment.*

Imaging Procedures and Image Evaluations:

*Upon Enrollment, each patient must undergo Depreotide Enhanced Scintigraphic Imaging. The resultant images will be evaluated both by on-site investigators and by three independent Blinded Readers who are experienced nuclear medicine practitioners.*

*The Inclusionary CT Scan will be read by the on-site Investigator and by three experienced radiologists who will serve as independent Blinded Readers for these Inclusionary CT Scan Images.*

*All Images - Depreotide and CT Scan - will be examined for the presence/absence of tumors/metastases in nine anatomical regions involving the lungs and the mediastinum/hilar areas. CT Images will be judged positive for a region if there is visualization of abnormality suggestive of tumor in the region. Depreotide Images will be considered positive for a region if there is significant focal uptake in the region.*

*Histopathology results will be available for at least one specified lesion per patient, - this lesion is designated the 'Main Presenting Lesion', and the identification of the approximate location of this lesion will be provided by the referring patient care provider to the surgeon, primarily on the basis of the unblinded, inclusionary Xray/CT scan results. However, it is the surgeon who will, post-biopsy, finally specify the precise anatomical region for this Main Presenting Lesion. (Communication from Sponsor - July 10 1998).*

*The Histopathology result, consisting of the specification of both a Region and a Disease Status for the Main Presenting Lesion, will constitute the Standard of Truth for all Efficacy evaluations. Thus, a Read of an Image will be judged to agree with Histopathology if and only if the Read agrees with Histopathology vis a vis Disease Status in the specific region in which the Main Presenting Lesion was located by Biopsy. (Sometimes an Adjacent region suffices -see below).*

Primary Endpoints:

Let S=Sensitivity (With respect to Histopathology for the Main Presenting Lesion)  
Sp=Specificity (With respect to Hisopathology for the Main presenting Lesion)  
p=Prevalence ( Within the Clinical trials, and for the Main Presenting Lesion )

Let

$$A = \text{Diagnostic Accuracy} = pS + (1-p)Sp$$

The Sponsor initially proposed Accuracy as the Primary Efficacy Endpoint. Comments from the FDA to the Sponsor ( April 15 1998 ) regarding FDA concerns as to the appropriateness of this Endpoint resulted in the Sponsor's communication ( May 15 1998 ) of the decision to modify the data presentation so as to " emphasize Sensitivity, Specificity, and Agreement in that order". It will therefore be assumed that, in decreasing order of importance:

*Sensitivity, Specificity and Accuracy are the Primary Endpoints.*

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(IV): *Critical Comments on the Design and its Implementation*

(1): The NDA submission presents, for the first time, a modification of the criterion of Concordance between Image and Histopathology. In all previous protocol submissions, and as detailed above in Section(II), the Depreotide Image Diagnosis was defined to agree with Histopathology if it agreed vis a vis Disease Status in the precise location specified by Histopathology for the Main Presenting Lesion. The Sponsor modified this criterion in the NDA submission as follows:

*Each Region is associated with several 'Adjacent' regions*

*A Depreotide Image diagnosis of Positive (Malignant) agrees with a histopathological diagnosis of Positive provided the Image Region presenting the positive diagnosis is either the same as the Region specified by histopathology, or is adjacent to this Region. Thus, for instance, a Depreotide Image diagnosis of malignancy in the Lower Right Lung will be considered as in agreement with a histopathologically specified malignancy in the Upper Right Lung.*

*A Depreotide Image diagnosis of Negative (Benign) agrees with a histopathological diagnosis of Negative provided the Image Region which corresponds to the histopathologically determined Region, along with all the regions on the Image which are adjacent to the histopathologically specified Region have been scored negative.*

Remarks:

This new criterion appears to be somewhat opportunistic. Clearly, if prevalence is high, which it is in these trials, then this new and more liberal criterion of Concordance, with its obvious capacity for increasing Sensitivities, ( all one needs now is significant focal uptake somewhere in a large neighborhood of the histopathologically located malignancy), will also increase Accuracy levels, while downplaying the clear possibility for Image Read inaccuracies in localization of abnormalities. There is also a downside to this new criterion, namely, it penalizes Specificities,- a histopathologically determined benign diagnosis for a Main Presenting Lesion located in the Lower Right Lung will be discordant with a Depreotide Image which presents focal uptake only in the Upper Right Lung. However, as mentioned several times above, disease prevalence is high in these trials, so that low Specificities do not seriously impact Accuracy levels. Consequently, given its post-hoc provenance, its distortion of Sensitivities and Specificities, and its bias towards greater Accuracy levels, this new criterion of Concordance will be presented in this report, but will not be assigned a privileged position.

(2): The Inclusion Criteria specify that biopsies should occur within six weeks of enrollment. It is natural to assume that these biopsies would be scheduled post-enrollment, but this was not the case for a considerable percentage of the patient population - 40% over the two pivotal trials. Biopsies which precede enrollment present the possibility of bias in patient selection; for instance, privileged enrollment of subjects with pre-enrollment verification of malignancies will bias Agreement levels upwards. Moreover, pre-enrollment biopsies present the possibility for modification of the appearance of lung tissue on the Images, which would introduce another source of bias. As it turns out, although Agreement levels for Image diagnostics were higher for the pre-enrollment biopsy population vis-a-vis the post-enrollment biopsy population, there was no corresponding shift in Sensitivities or Specificities, and therefore the Reviewer has determined that, provided Sensitivities and Specificities take precedence over Agreement levels, there was no need to truncate the evaluable patient population down to the smaller class of subjects for whom Enrollment preceded Biopsy.

(3): The most current amended Protocol is dated December 8 1997. There were several earlier protocols, in particular there were protocols dated March 10 1997 and July 14 1997. The July 14 protocol amended the principal statistical criterion for success in Agreement found in the March 10 protocol as follows:

March 10 1997 - Accuracy level=.8  
July 14 1997 - Accuracy level=.7

Again, this modification appears opportunistic. The clinical trials were well advanced by July, and the statistics from these ongoing trials would suggest .7 as an easily attainable Accuracy level. The more liberal July 14 Adjacent Region Agreement criterion is therefore suggestive of the possibility of a post-hoc, data driven modification of an initial hypothesis which can no longer be met. This possibility provides yet another reason to ignore Accuracy levels as endpoints. Of course, since the Sponsor provided only an Accuracy Level statistical criterion, ( Null hypothesis: Accuracy=.7 ), with no corresponding statistical criteria for Sensitivity and Specificity, the Reviewer is reduced to purely 'commenting' on the significance of the actual Sensitivities and Specificities achieved in these trials rather than to 'verifying' hypotheses concerning these Endpoints.

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(V): Reviewer's Statistical Tables and Analyses

Several Statistical Tables are included below. Each table will be described and commented upon.

Table(I): This table provides comparisons of Sensitivities, Specificities and Accuracies for Depreotide Image Reads for several subclasses of subjects. The intention here is to determine if the subclasses of major concern - subjects whose biopsies preceded Enrollment, subjects whose Cscans presented a Solitary Pulmonary Nodule, - produce Sensitivities, Specificities or Accuracies which differ significantly from one another or from the full class statistics.  
 Note: All measures are calculated with respect to Majority Reads as defined earlier.

Table (I)  
 Diagnostic Statistics

( Note - all probabilities are presented as percentages )

34A=Clinical Trial P829-34A 34B=Clinical Trial P829-34B Comb= 34A and 34 B combined

TRIAL	CATEGORY	N	PR	S	S*	SP	SP*	AGR	AGR*
34A	Early BIO	31	94	66	86	50	0	65	81
	NODULE	65	68	61	73	86	67	69	71
	ALL	112	75	70	82	86	61	74	77
34B	Early BIO	60	93	73	88	100	75	75	87
	NODULE	62	90	68	84	83	67	69	82
	ALL	114	88	71	85	79	57	72	82
Comb	Early BIO	91	93	71	87	83	50	71	85
	NODULE	127	79	65	79	85	67	69	76
	ALL	226	81	71	84	83	60	73	79

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Categories are:

Early BIO = Subjects whose Biopsies preceded Enrollment

NODULE = Subjects whose Main Presenting Lesion was classified as a Solitary Nodule

ALL= All Subjects in the indicated Trial

N=Sample Size for the Category

S=Sensitivity for the 1-1 Analysis; S\*=Sensitivity for the Adjacent Region Analysis

Sp=Specificity for the 1-1 Analysis; Sp\*=Specificity for the Adjacent Region Analysis

AGR= Agreement level (Accuracy) for the 1-1 Analysis

AGR\*=Agreement Level (Accuracy) for the Adjacent Region Analysis

Comments on Table(I):

(1): There is little variation in the nine values listed under each of the variables S, S\*, Sp, Sp\*, AGR, AGR\* . An exception is SP and SP\* under Early Bio, but the exceptional values here - 50, 100, 0, 75 - are due to the extremely small sample sizes ( For instance, Early Bio 34A, with a prevalence of 94%, contributes only 2 subjects for the SP calculation). Given the stability of values within columns in all instances where sample sizes permit any confidence in these values, it is clear that neither the Early Bio subclass nor the Nodule subclass needs to be analyzed separately. This logic can be carried a step further - from subclass statistics to trial statistics: there is no significant difference from 34A to 34B to ALL for each of the statistics S, Sp etc, so that, for presentation purposes, further discussion of these statistics could be, and, for the most part will be, restricted to their values for the combined trials (ALL). Note: (This simplification in the presentation of results is not to be construed as suggestive of the adequacy of a single trial, rather than both trials, for the drawing of conclusions. Both trials are necessary).

(2): As would be expected, S\* is larger than S, and Sp\* is smaller than Sp. Clearly, Sensitivities are likely to increase if Image Abnormalities ( significant focal uptake ) in regions adjacent to the histopathologically determined region of malignancy are considered confirmatory of that malignancy. Likewise, Specificities are likely to decrease if Image Abnormalities in regions adjacent to the region found to be benign by histopathology are considered confirmatory of malignancy. Note, in particular, that the decrease from Sp to Sp\* appears to present a distinct disadvantage for use of the Adjacent Algorithm, since the Sponsor's rationale for these studies, with its implicit focus on a Specificity related concern, namely on the potential for Depreotide Images to correctly signal when Cscan abnormalities are benign, receives negative support from these lowered Specificities. *Presumably, the Sponsor's original Primary Endpoint of Diagnostic Accuracy (AGR) was intended to strike a balance between Specificities and Sensitivities, but the high prevalence rates in these trials cause Diagnostic Accuracy to be virtually identical with Sensitivity, and highly insensitive to the potentially much more significant Specificity.*

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Table(II): The Pivotal Trials 34A and 34B required an Inclusionary Unblinded Cscan Read, which was typically positive. There were three subsequent Blinded Cscan Reads, but these Reads, perhaps initially intended as Comparator Reads to Depreotide Image Reads, were not used as such in any significant way in the final NDA submission. This de-emphasis makes sense, given that Unblinded Cscans were an essential element among the Inclusionary Criteria. Moreover, all of the Primary Efficacy Endpoints - Sensitivity, Specificity, Agreement - involve only Depreotide Reads and the Standard of Truth (Histopathology), so that the Blinded Cscan Reads could, in fact, be ignored in this Review. On the other hand, given the absence in these trials of explicit hypotheses on Sensitivities and Specificities reflective of 'success' of Depreotide Reads taken alone, and given the Sponsor's explicit rationale for Depreotide Reads as potential sources for differential diagnoses on subjects who are suspicious of lung cancer largely on the basis of Cscan Reads, it would make sense to investigate possible diagnostic 'synergisms' between Cscans and Depreotide Images. In this Review the candidate Cscan Read for this investigation was chosen to be the majority 'best case' Blinded Read. That is, the Blinded Cscan Reads were first modified so that missing values among the three Reads were rendered concordant with the Standard of Truth, and then the majority Read was chosen. It was felt that this Majority Blinded Read, in that it reflected no greater a priori knowledge than the Majority Depreotide Image Read, was more appropriate than the Inclusionary Unblinded Cscan Read for investigations of combined Cscan-Depreotide Image diagnoses. The possibility exists, a priori, that this majority 'best case' Cscan Read differs appreciably from the Unblinded Inclusionary Cscan Read. However, Table(II) below indicates that these two diagnoses are highly correlated.

Table(II)  
 Comparison of Unblinded Cscan Read to Majority Blinded 'best case' Cscan Read  
 (Table entries are Frequencies)

	STUDY A			STUDY B			COMBINED	
	CMAJ=0	CMAJ=1		CMAJ=0	CMAJ=1		CMAJ=0	CMAJ=1
C=0	7	6		5	9		12	15
C=1	6	93		6	94		12	187

C=Unblinded Inclusionary Cscan Read Diagnosis of Main Presenting lesion

CMAJ=Majority 'best case' Blinded Read diagnosis of Main Presenting Lesion

Note the following reasonably strong indicators of Agreement between C and CMAJ:

KAPPA(Study A)=.48

KAPPA(Study B)=.33

KAPPA(Combined)=.40

Agreement=.89

Agreement=.87

Agreement .88

Tables (III) and (IV): The Blinded majority 'best case' Cscan Reads are compared to the Blinded majority 'worst case' Depreotide Image Reads.

Table (III)  
Comparisons of Diagnostic Statistics for Depreotide Image vs Cscan for the 1-1 Algorithm  
( All entries are Percentages )

	S(IMAJ)	S(CMAJ)	Sp(IMAJ)	Sp(CMAJ)	A(IMAJ)	A(CMAJ)
STUDY A	70	90	86	18	74	72
STUDY B	71	95	79	43	72	89
COMBINED	71	93	83	26	73	81

Table (IV)  
Comparisons of Diagnostic Statistics for Depreotide Image vs Cscan for the Adjacent Algorithm  
( All entries are Percentages )

	S(IMAJ)	S(CMAJ)	Sp(IMAJ)	Sp(CMAJ)	A(IMAJ)	A(CMAJ)
STUDY A	82	95	61	4	77	72
STUDY B	85	96	57	7	72	85
COMBINED	84	96	60	5	73	79

IMAJ refers to Majority 'worst case' Blinded Depreotide Image Read

CMAJ refers to Majority 'best case' Blinded Cscan Image Read

S=Sensitivity Sp=Specificity A=Diagnostic Accuracy

Comments: The most significant results in these tables are:

- (a): Depreotide Images provide greater Specificity
- (b): Depreotide Images do not outperform Cscan Images vis-a-vis Accuracy levels

Table(V) and Table(VI): These tables provide a within-patient Comparison of Depreotide Images with Cscans, stratified by Histopathological Outcome.

Table (V)

H=0

( No Disease 42 Subjects Entries are Frequencies Studies 34A and 34B are combined)

One-One	CMAJ=0	CMAJ=1		Adjacent	CMAJ=0	CMAJ=1
IMAJ=0	8	27		IMAJ=0	0	25
IMAJ=1	3	4		IMAJ=1	2	15*

Table (VI)

H=1

( Disease 184 Subjects Entries are Frequencies Studies 34A and 34B are combined )

One-One	CMAJ=0	CMAJ=1		Adjacent	CMAJ=0	CMAJ=1
IMAJ=0	7	47		IMAJ=0	2	28
IMAJ=1	6	124		IMAJ=1	6	148

IMAJ=Majority 'worst case' Blinded Depteotide Image Read

CMAJ=Majority 'best case' Blinded Cscan Read

Reviewer's Comments:

The principal feature of both tables above is the lopsidedness of the off-diagonal entries. That is, given a discordance in Reads between Depreotide Images and Cscans, the Cscan Read is much more likely to score positive. This feature is consistent with the fact that most patients qualify for this Study on the basis of positive Cscans, regardless of true disease status. *In particular, for healthy patients, the Depreotide Read is more closely concordant with truth.*

Table(VII)and Table(VIII): These tables provide another look at the joint performance of Depreotide Images and Cscans.

Table(VII) lists the subject frequencies for Histopathology results for various combinations of Cscan and Depreotide Image Reads for the combined trials. In these combined trials the prevalence rate is .80, so that the appearance of the table is at least partially driven by this preponderance of malignancies.

Table(VIII) is the analogue of Table(VII) for the case where prevalence =.50. This table was generated by the Reviewer through repeated compilation of approximately 84 subjects - 42 healthy, 42 diseased - with the 42 positive subjects randomly selected from among the 184 available positives.

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

	One-One Algorithm			Adjacent Algorithm	
	H=0	H=1		H=0	H=1
CMAJ=0 IMAJ=0	8	7		0	2
CMAJ=0 IMAJ=1	3	6		2	6
CMAJ=1 IMAJ=0	27	47		25	28
CMAJ=1 IMAJ=1	4	124		15	148

Table (VIII)  
Diagnostic Capacity of Images/Cscans Taken Together  
(42 random positives joined with the 42 negatives)

	One-One Algorithm			Adjacent Algorithm	
	H=0	H=1		H=0	H=1
CMAJ=0 IMAJ=0	8	1		0	0
CMAJ=0 IMAJ=1	3	1		2	1
CMAJ=1 IMAJ=0	27	12		25	7
CMAJ=1 IMAJ=1	4	28		15	32

Note:

CMAJ=Majority 'best case' Blinded Cscan Read

IMAJ= Majority 'worst case' Blinded Depreotide Read

H= Histopathology result

*Comments on Tables(VII) and (VIII):*

*If Depreotide Images functioned as definitive differential aids to Cscans in lung tumor diagnoses, all the rows in the tables above would have the character of the fourth row of Table(VII), namely there would be a strong imbalance in entries under the H column, so that any particular CMAJ, IMAJ combination would be highly correlated either with  $H=0$  or with  $H=1$ . As it stands, only Row#4 of table(VII), with its message that the simultaneous positivity of Cscan and Depreotide images is strongly indicative of malignancy, possesses this property. However, this result could be significantly conditioned on the fact that prevalence is extremely high. As is clear from Table(VIII), the strength of the conclusion that  $H=1$  given that  $CMAJ=IMSAJ=1$  is tempered by lower prevalence rates. Of particular interest is the fact that Table(VII) provides no strong evidence that negative Depreotide Images, in conjunction with positive Cscans, could constitute trustworthy evidence that the Cscan abnormality is benign in circumstances of high prevalence of disease. Table(VIII) points to the possibility that negative Depreotide Images might be reasonably indicative of benign conditions in situations where prevalence is not too large; however, the results are at most suggestive. Consequently, an essential part of the Sponsor's stated rationale for these Studies, which includes the statement that Depreotide Images could potentially provide a non-invasive means of characterizing lung lesions so as to avoid biopsy, meets with no significant supporting evidence here.*

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ON ORIGINAL

(VI): Statistical Reviewer's Final Comments/Conclusions:

*There is reasonably strong evidence to support the use of positive Depreotide Images as a Second Line Diagnostic corroborative of lung malignancies in clinical contexts where lung malignancies have high prevalence rates and where standard diagnostic modalities - Cscans/Xrays - have previously presented some evidence of lung malignancy. However, in cases of this nature, where initial, conventional diagnoses would, in themselves, indicate the need for biopsy, Depreotide Imaging provides, at most, a reinforcement of the decision to biopsy. Moreover, no significant evidence is provided in these trials to support reliance on negative Depreotide Image Diagnostics as indicative of true disease state under any circumstances. Consequently, there is no clear evidence in these trials which would be supportive of the utilization of Depreotide for the differential detection of malignant tumors of the lung. Perhaps the difficulty here lies with the fact that both the Cscan and the Depreotide Reads were, for the purposes of the Sponsor's chosen statistical analyses, principally characterized as Positive/Negative, without any additional emphasis given to the particular anatomical and/or physiological 'features' of the Reads. The joint occurrences of such features, - tumor sizes on Cscans combined with graded intensities of focal uptake on Depreotide Images, etc, - could conceivably function as paired 'covariates' which might be significantly correlated with Histopathology. If a study of such paired sets of 'covariates' were to prove significantly correlated with histopathology, a clearer picture could emerge concerning circumstances under which Depreotide Images provide differential diagnostic utility when combined with Cscans.*

/S/ 11/23/98

A G Mucci, Ph.D.  
Statistical Reviewer

Concur:

/S/ 11/23/98

Mahboob Sobhan, Ph.D.  
Acting Team Leader

/S/ 11/23/98

Michael Welch, Ph.D.  
Acting Deputy Director

Cc:Archival NDA#21-012  
HFD-160/E. Jones/S Loewke  
HFD-160/C Ferre-Hockensmith  
HFD-160/File Copy  
HFD-715/E. Nevius/M. Welch/M. Sobhan/A. Mucci

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 021012**

**MICROBIOLOGY REVIEW(S)**

HFD-160/Hackenmitt

REVIEW FOR HFD-160  
OFFICE OF NEW DRUG CHEMISTRY  
MICROBIOLOGY STAFF  
MICROBIOLOGIST'S REVIEW #3 OF NDA 21-012  
16 February 1999

A. 1. NDA 21-012 BZ

APPLICANT: Diatide, Inc.  
9 Delta Drive  
Londonderry, NH 03053

2. PRODUCT NAMES: Kit for the Preparation of Technetium Tc 99m  
Depreotide Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:  
The product is an injectable imaging agent.

4. METHODS OF STERILIZATION:

[REDACTED]

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE  
INDICATION:

The product is used for scintigraphic imaging of malignant tumors in  
the lung.

B. 1. DATE OF INITIAL SUBMISSION: 15 June 1998

2. DATE OF AMENDMENT: 21 January 1999 (Subject of this  
Review)

3. RELATED DOCUMENTS: IND [REDACTED]  
DMF [REDACTED]

4. ASSIGNED FOR REVIEW: 16 February 1999

C. REMARKS: The submission is a new NDA for a kit for the preparation  
of Technetium Tc 99m Depreotide injection. The kit is  
not preserved and is in a unit dose configuration. The  
drug product is manufactured by Dr. Rentschler  
Biotechnologie GmbH (Laupheim, Germany).

D. CONCLUSIONS: The application is recommended for approval on the

[Redacted]

[Redacted] /S/ [Redacted] 16 February 1999  
Paul Stinavage, Ph.D.  
[Redacted] /S/ [Redacted] 2/21/99

cc: Original NDA 21-012  
HFD-160/C. Ferre-Hockensmith/R. Harapanhalli  
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 16 February 1999  
R/D initialed by P. Cooney

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ON ORIGINAL

HFD-160/Hackensmeth

REVIEW FOR HFD-160  
OFFICE OF NEW DRUG CHEMISTRY  
MICROBIOLOGY STAFF  
MICROBIOLOGIST'S REVIEW #2 OF NDA 21-012  
18 November 1998

A. 1. NDA 21-012 BI

APPLICANT: Diatide, Inc.  
9 Delta Drive  
Londonderry, NH 03053

2. PRODUCT NAMES: Kit for the Preparation of Technetium Tc 99m  
Depreotide Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:  
The product is an injectable imaging agent.

4. METHODS OF STERILIZATION:

[REDACTED]

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE  
INDICATION:

The product is used for scintigraphic imaging of malignant tumors in  
the lung.

B. 1. DATE OF INITIAL SUBMISSION: 15 June 1998

2. DATE OF AMENDMENT: 4 November 1998 (Subject of this  
Review)

3. RELATED DOCUMENTS: IND [REDACTED]  
DMF [REDACTED]

4. ASSIGNED FOR REVIEW: 17 November 1998

C. REMARKS: The submission is a new NDA for a kit for the preparation  
of Technetium Tc 99m Depreotide injection. The kit is  
not preserved and is in a unit dose configuration. The  
drug product is manufactured by Dr. Rentschler  
Biotechnologie GmbH (Laupheim, Germany).

D. CONCLUSIONS: The application is approvable pending resolution of microbiology concerns.

[Redacted]

APPEARS THIS WAY  
ON ORIGINAL

[Redacted] /S/

18 November 1998

Paul Stinavage, Ph.D.

[Redacted] /S/

11/19/98

cc: Original NDA 21-012  
HFD-160/C. Ferre-Hockensmith/R. Harapanhalli  
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 18 November 1998  
R/D initialed by P. Cooney

APPEARS THIS WAY  
ON ORIGINAL



D. CONCLUSIONS: The application is approvable pending resolution of microbiology concerns

[Redacted]

[Redacted] /S/

Paul Stinavage, Ph.D.

4 August 1998

[Redacted] /S/ 8/11/98

cc: Original NDA 21-012  
HFD-160/K. Colangelo/R. Harapanhalli  
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 4 August 1998  
R/D initialed by P. Cooney