CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020887

STATISTICAL REVIEW(S)

JUN 11 1998

STATISTICAL REVIEW - PROTOCOL EVALUATION

NDA:	20-887
Trade Name:	Acutect (Kit for the preparation of Tc 99m Apcitide)
Sponsor:	Diatide, Inc.
Indications:	Detection and Localization of Acute Venous Thrombosis.
Medical Officer:	Joseph Zolman, M.D., HFD-160
Project Manager:	Catalina, HFD-160
Submission Date:	3/30/1998

APPEARS THIS WAY ON ORIGINAL

The sponsor submitted protocols for two Phase IV outcome studies of Acutect in detecting acute venous thrombosis (DVT).

APPEARS THIS WAY ON ORIGINAL

Protocol 280-40

The sponsor will conduct a prospective cohort study in which patients with suspected acute VT but w/o prior history of DVT, will undergo Acutect scanning followed by Compression Ultrasound (CUS) to determine the presence or absence of acute VT.

The objectives of this study is to evaluate the sensitivity, specificity, and predictive values of AcuTect in assessing patients suspected of acute venous thrombosis in the lower extremities.

A total of 400 patients with suspected acute VT will be enrolled in this study. Each eligible patient will undergo AcuTect scanning followed by CUS. Patients who are positive on both AcuTect and CUS will be followed-up at 3-month. Patients who are negative on both Acutect and CUS, will undergo repeat CUS at day 6-8. When both AcuTect and CUS results are discordant, venography will be performed for definitive diagnosis of DVT and will be followed-up at 3-month.

The results will be adjudicated as normal, abnormal or indeterminate by a central committee and will be used in the final analysis.

The sponsor primary analysis plan includes estimation of sensitivity, specificity, and predictive values of AcuTect compared to CUS and venography.

We have the following concerns that should be communicated to the sponsor for clarification:

1. Why Acutect will be followed by ultrasound in order? Why not randomize?

2. What's the rationale to compare Acutect primarily with ultrasound as opposed to venography that was used as comparator in Phase III studies?

3. What's the final endpoint? Is it at the end of three month follow-up or at the time of initial evaluation?

4. In case a patient is AS-/CUS-, a repeat CUS will be done and if the patient is AS-/CUS+ at the end of the follow-up period, what will be the diagnosis for this patient? Will that patient be a discordant and therefore will undergo Venography or will be considered false negative?

5. What was meant by heterogeneous group of outcomes? (Section 5.0, statistical considerations).

6. Clarify the criteria to classify patients as VTE + or VTE - for analysis as per schema on page 4 (section 4.1.2). Clarify how patients will be classified in terms of treatment algorithm.

7. We suggest independent reading for all procedures to avoid bias.

8. What is meant by the key accuracy index is the neg. Predictive value?

9. What is the assumed negative predictive value used in the sample size estimation?

10. Why primary objective is negative predictive value while the primary analysis is the sensitivity, specificity etc.?

Protocol 280-41

In this protocol, the sponsor plans to assess the outcome of Acutect, D-dimer and Imipedance Plethysmography (IPG) in patients with signs and symptoms of Acute Recurrent Deep Vein Thrombosis.

The objective of this study is to obtain preliminary information regarding management algorithms and predictive values of AcuTect.

A total of 50-100 patients will be enrolled in this study. Each patient will undergo AcuTect scanning first, followed by D-dimer and IPG. Patients who are negative on all three procedures will be followed-up at month 3. Patients who are positive in al least one procedure, will undergo contrast venography and will also be followed-up at month 3.

For the primary analysis, the results of all procedures will be

adjudicated by a central committee. The sponsors analysis plan includes estimation of sensitivity, specificity of Acutect compared to D-dimer, IPG, and venography.

This reviewer has the following concerns:

(1) The objective of this study was not clear. The population in this study includes patients with prior history of DVT. It was not clear why D-dimer and IPG will be used as comparator in this study.

(2) The adjudication by a central committee is not an acceptable method of evaluation. Blinded reading is required for an unbiased evaluation.

(3) The protocol should have more details on sample size estimation.

Comments:

We have discussed the above issues along with MO's comments in a T-con and requested that a detailed protocol is submitted for our evaluation.

/S/ 6/11/98

Mahboob Sobhan, Ph.D.
Reviewing Statistician, HFD-720

Concur: Michael Welch, Ph.D.

cc:
Archival NDA 20-887
HFD-160/File copy/Dr. Jones/Dr. Zolman/Ms. Ferre
HFD-720/ File copy/Dr. Welch/Dr. Sobhan

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STATISTICAL REVIEW AND EVALUATION

NDA:	20-887
Priority:	1P
Trade Name:	Acutect (Kit for the preparation of Tc 99m Apcitide)
Sponsor:	Diatide, Inc.
Indications:	Detection and Localization of Acute Venous Thrombosis..
Date:	Received by Biometrics - 8/28/97
Medical Officer:	Joseph Zolman, M.D., HFD-160
Project Manager:	Catalina Ferre-Hockensmith , HFD-160
User Fee Goal Date:	2/20/97

Summary: The sponsor seeks approval of Technetium Tc 99m P280, a radiolabeled peptide, in the detection and localization of acute venous thrombosis (VT) in patients who are suspected of acute VT. Currently, the diagnosis of venous thrombosis is based on imaging studies with doppler ultrasound or contrast venography (CV) in conjunction with clinical signs and symptoms. In this application, the sponsor claims that Tc 99m P280 binds to the activated platelets which enables visualization of lesions characterized by activated platelet involvement postulated to be present in recent or active thrombus formation, thereby detecting acute VT. The sponsor also claims that it has a better safety profile than CV. To support these claims, the efficacy and safety of Tc 99m P280 were evaluated in three pivotal Phase III studies in addition to other Phase II/III studies. The *efficacy endpoint* was the independent blindly-read agreement rate (percent detected positive or negative for VT) of Tc 99m P280 with CV as 'standard of truth'. The objective was to demonstrate that the agreement rate of Tc 99m P280 is 60% or better (rejecting the null hypothesis that Tc 99m P280 agreement rate with CV is less than 60%). Results of two pivotal efficacy studies demonstrate that there were large variations between studies (45% vs. 82% in study A and B, respectively) in detecting acute VT by blindly-read CV, the 'standard of truth'. The strength of agreement between Tc 99m and CV was poor (kappa < 0.40) in both studies. The null hypothesis was not rejected according to 3 out of 6 blinded reader evaluations in study A, and none of the 6 blinded reader evaluations in study B resulted in no statistically significant agreement. The results of post-hoc subgroup difference analyses, i.e., chronic (with history of VT or pulmonary embolism) *vs.* acute (no prior history of VT or PE), appeared to demonstrate that the agreement rate was statistically significantly ($p<.05$) higher in acute patients than the chronic patients, although this assertion was not proven by clinical manifestations in the pivotal studies . The incidence of adverse events reported in all patients who were exposed to Tc 99m P280 was slightly over 5% (mostly pain and headache). There were no trends either in vital signs (except drop in pulse rate), hematology or chemistry values post-injection, although clinically abnormal changes (below or above the normal range) were seen in liver enzymes. Patients with abnormal changes in liver enzyme values also had abnormally high baseline values. These changes appeared to be attributable more to underlying diseases rather than to Tc 99m P280. Overall, as per protocol, study A demonstrated weak evidence that Tc 99m P280 detects VT at least 60% of the time, while study B demonstrated no evidence for that conclusion.

Key Words: Diagnostic Agreement, acute/chronic VT, Subgroup analyses.

Table of Contents

1.0 INTRODUCTION

1.1. Background

This NDA is in support of Technetium Tc 99m P280, a radiolabeled peptide, in the detection of acute venous thrombosis (VT) compared to contrast venography (CV). Contrast Venography, in conjunction with clinical sign and symptoms is often the current practice to detect VT. This modality provides anatomical information but not functional information, i.e., can not distinguish between new developing thrombus and old thrombus. In this application, the sponsor claims that Tc 99m P280, a radiolabeled peptide, binds to activated platelet involvement, thereby aiding in the detection of disorders characterized by activated platelet involvement such as acute VT.

The review will first describe the pivotal studies that will support the indication sought followed by highlighting study limitations (if any) or issues that need to be addressed based on the data submitted in this application.

1.2. Indication

The sponsor proposes the indication for the use of Acutect as follows:

"Acutect™ is indicated for scintigraphic imaging of acute venous thrombosis".

1.3. Overview of Studies

The sponsor has conducted eleven studies (as shown below) in the development of Acutect in a total of 684 subjects of which 602 were suspected VT patients.

Study #	Phase	Total Subjects	VT Patient	Control Standard	Objective
280-00	II	9	9	Uncontrolled	Narrative efficacy
280-01	II	26	--	Uncontrolled	To study other indication
280-20	II	31	12	Uncontrolled	Dose-ranging
280-21	II	30	7	Uncontrolled	To study active platelets
280-22	II	28	28	Doppler Ultrasound	Dose-ranging
280-23	II	14	--	Uncontrolled	Other indication
280-30	III	135	135	Doppler Ultrasound	Efficacy + safety
280-31	III	22	22	Institutional Dx.	Radionuclide Ventriculography
280-32A (Pivotal)	III	135	135	Contrast Venography	Efficacy + limited safety
280-32B (Pivotal)	III	145	145	Contrast Venography	Efficacy + limited safety
280-33 (Pivotal)	III	109	109	Institutional Dx.	Safety + limited effic.

Studies 280-20 and 280-22 provided supporting evidence for the varying doses of Technetium Tc 99m radioactivity and P280 peptide levels. Study 280-30 was originally initiated to assess the overall efficacy of Tc 99m P280 compared to institutional diagnosis (based mostly on doppler ultrasound) as the standard. But the study was discontinued after enrolling 135 patients as per Divisions recommendation that doppler ultrasound was not an appropriate standard. This study should provide some insight in terms of diagnostic performance when ultrasound was used as comparator. Studies 280-32A and B were considered pivotal efficacy studies and study 280-33 was considered a pivotal safety study.

1.4. Review Issues

During a Phase III progress meeting with the sponsor, the statistical plan was discussed and we raised the concern that although agreement rate as primary endpoint is appealing, it does not differentiate between positive and negative test results. But the sponsor insisted on agreement rate since the study design would use an active comparator (contrast venography) instead of 'truth', in which case sensitivity and specificity would have been a better choice. We suggested that in an active comparator trial, the agreement rate should be based on blindly read test scans vs. blindly read contrast venography rather than unblindly read test scans or contrast venography to avoid bias. We also reminded the sponsor that contrast venography itself is not an accurate test, therefore, the effect of reference test error may also bias the final outcome.

This NDA was discussed with the clinical reviewers in terms of the indication sought, i.e., detection and localization of acute venous thrombosis. During the team discussion, it appeared that we needed some information or features that are captured in this application to evaluate the ability of Tc 99m P280 in distinguishing between chronic and acute cases. Specifically, the clinical reviewer raised the issue whether Tc 99m P280 can characterize between *phlebitis* and active clot in the limb. The sponsor claims that Tc 99m P280 is a radiolabeled peptide which binds to the activated platelet and consequently, it should be useful in detecting active clots.

In one study (280-30), the sponsor's results suggested some evidence of greater accuracy of detecting VT in acute patients (defined acute who had no history of VT or PE) than in chronic (who had history of VT or PE) patients. Due to the weak efficacy (agreement of Tc 99m P280 with contrast venography) based on blinded reads in the pivotal trials, the sponsor raised the issue that unblinded (in the presence of patient's clinical signs and symptoms and medical history) evaluation should be considered for the efficacy evaluation as opposed to blinded evaluation since clinical venograms are often read in conjunction with patients clinical history in diagnostic imaging practice.

In view of the above and additional concerns that came up during team meetings, this review will focus on the following points:

(i) Dose-response evaluation of Tc 99m P280 to support the suggested 100 μg,

20 mCi dose.

(ii) Independence of the pivotal studies in terms of site ~~inve~~stigators and blinded readers who evaluated the images.

(iii) Efficacy of Technetium Tc 99m P280 between chronic and acute VT patients.

(iv) Consistency of efficacy results across studies, in major subgroups, and between blinded and unblinded read evaluation.

(v) Comparison of agreement rates between Doppler ultrasound and Contrast Venography.

(vi) Evidence of better safety profiles for Tc 99m P280 compared to Contrast Venography.

2.0. EVALUATION

Our evaluation included verifying the sponsor's results (using data submitted with the application), verifying the appropriateness of sponsor's analytic methods, using alternative statistical methods where necessary, and verifying the consistency of the results across studies.

2.1. DOSE-RESPONSE

Dose-response studies were conducted to evaluate the optimal dosage of Tc 99m P280. A combination of optimal peptide and radioactive levels were studied primarily in study 280-22, although an attempt was also made to evaluate optimal dosage of radioactivity level in study 280-20. Since the sponsor claims that study 280-22 provides the primary support, our review will focus on this study and will refer to the findings of study 280-20 as deemed necessary to highlight the consistency in the findings.

2.1.1. Description of Dose-Response Study

Study 280-22 was designed as a prospective study where patients were randomized in a 3x3 factorial layout of a single administration of Technetium Tc 99m P280 at one of three levels of P280 peptide (20, 50, 100 μg) and one of three levels of Tc 99m radioactivity (5, 10, or 20 mCi). The objective of the trial was to assess the dose-related response in agreement rate in detecting acute VT by Tc 99m P280 images (blindly read by three readers) confirmed by Doppler Ultrasound (considered standard of truth and evaluated unblindly at the investigational site) at three levels of peptide and radioactivity. In addition, the region of interest (ROI) analyses were to be performed blindly after all image analyses had been complete.

The protocol called for a total of 36 patients at four 4 centers but the study actually enrolled 27 patients at three centers due to lack of enrollment at one center.

2.1.2. Results of Dose-response Study

A total of 27 patients were evaluable for dose-response, i.e., agreement rate by peptide and radioactivity level analyses. All but one patient had signs and symptoms of suspected VT at enrollment. Using Doppler ultrasound (the standard of truth) the investigators diagnosed all patients as positive for VT. Therefore, the agreement rate was the percentage of patients for whom Tc 99m P280 was also diagnosed VT in the same region(s) or collateral region(s).

Figure 1 shows the agreement rate at three doses of P280 peptide (20, 50, 100 μg) and three levels of radioactivity (5, 10, 20 mCi) based on three blindly read evaluations of Tc 99m P280 images vs. Ultrasound. The agreement rate appeared to be higher for higher peptide level as per read 1 and read 3, though differences between peptide levels were not statistically significant ($p>.15$). There are no significant differences in response rate between radioactivity levels. Both 10 mCi and 20 mCi appeared to generate higher but similar response rates than the 5 mCi level. The mean ROI was higher for 20 mCi level and statistically significantly different ($p<.05$) than either 5 mCi or 10 mCi level. There were no differences in ROI by peptide levels.

In an earlier Phase II study (study 280-20, not discussed in this review) involving 21 evaluable patients, evaluating agreement rate by radioactive levels, a higher response rate was also noted at 20 mCi than either 10 or 30 mCi.

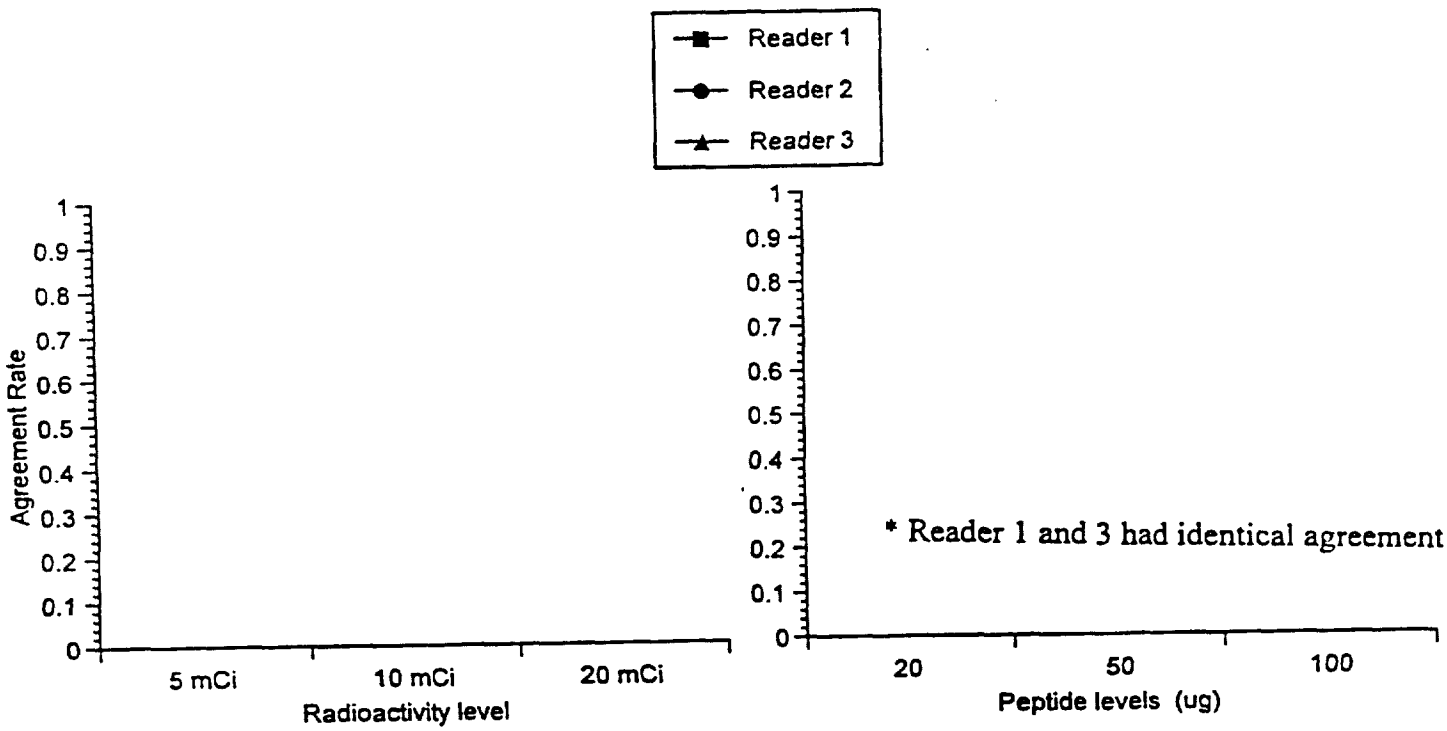

Figure 1: Dose-Response Curve for the Agreement Rate by Peptide and Radioactivity level, Study 280-22.

i) *Technetium Tc 99m Images (Read 1)*: In the first read, three independent experienced nuclear medicine physicians (reader 1,2,3) blindly evaluated the image-sets as per protocol:

- Images stripped of all patient information, the institution or the inclusion/exclusion criteria..
- Images at 10, 60, and 120-180 minutes post-injection were combined and displayed in the same session.
- Each of 9 regions, i.e., right calf, right knee, right thigh, right iliac, inferior vena cava, left iliac, left thigh, left knee, and left calf were evaluated and graded for the presence (positive) or absence (negative) of VT. An indeterminate score was assigned if no diagnosis could be made.

ii) *Technetium Tc 99m Images (Read 2)*: In the second read, another set of three independent nuclear medicine physicians (reader 4, 5, 6) blindly evaluated the images as in read 1 but separately for each time point first, and then for the combined image-sets.

iii) *Contrast Venography (Truth)*: To determine the 'standard of truth', contrast venography was read in three different ways as follows:

- **Blind read:** Three independent readers who did not participate in any other capacity in the study were to blindly evaluate the venograms at each region similar to read 1. Truth for each body region was derived as the majority result of the three readers readings.
- **Unblind Read:** The same images were interpreted by the participating radiologists at the institution in the context of each patients clinical history.
- **Blind Read (Hamilton):** Three separate physicians who were experienced in vascular medicine and venography at Hamilton Civic Hospital Research Center in Ontario, Canada, evaluated the images separately and made a consensus read as the standard of truth.

Efficacy Measures: The *primary* efficacy endpoint was the patient-based agreement rates between the blinded reads of contrast venography and blindly read evaluations of Technetium Tc 99m P280 results. At the patient level diagnosis, a patient was considered having VT if Tc 99m was positive in at least one region or contiguous region in common with the CV diagnosis region(s).

The *secondary* endpoints were sensitivity and specificity based on blinded reads, and agreement rates between the unblinded reads.

Stated Hypothesis and Sample Size: The null hypothesis was that the blinded read agreement rates between the Technetium Tc 99m and the contrast venography in detecting VT is at least 60%. The sponsor's goal was to reject the null in favor of the agreement rates that exceeds 60%.

2.1.3. Comments on Dose-Response

The study enrolled only 27 patients with only three patients in one of nine peptide and radioactive level combination. Based on this small sample size, no definitive dose-response relationship could be evaluated though the study suggests some upward trend in response at higher peptide levels than radioactive levels. There was a trend towards higher agreement rates with ascending doses of the peptides but not with radioactive doses. The study did show some statistically significant changes in hematology, clinical chemistry, and vital sign parameters following Tc 99m P280. The pivotal Phase III safety study that will be reviewed in the subsequent section may provide additional information on the safety profiles.

2.2. EFFICACY

The sponsor initiated Phase III efficacy study 280-30 where technetium Tc 99m P280 images were judged against results of final independent institutional diagnosis using mostly doppler ultrasound. Since ultrasound is not considered a standard of truth for diagnosis of VT by the Medical Division, two more pivotal efficacy studies, study 280-32A and study 280-32B, were conducted. In this review, the primary and secondary efficacy evaluation will be based on the results of the two pivotal studies. To address the review issues (ii) and (v) in section 1.4, results of study 280-30 will also be evaluated.

2.2.1. Description of Phase III Efficacy Studies

Design: Studies 280-32A and 280-32B were designed as prospective, single-dose, within-patient (each patient was to get both procedures) studies of Technetium Tc 99m P280 compared to contrast venography (each study followed separate but identical protocols). Patients who were at least 18 years old and within *10 days of onset of significant signs and symptoms of suggestive VT (Acute)*, were eligible for Technetium Tc 99m P280 imaging either before or after contrast venography within 36 hour period.

Objectives: The primary objectives of these two trials were to evaluate the efficacy of Tc 99m P280 scan compared to contrast venography in detecting acute VT and to evaluate in a limited scope, the safety profiles of Tc 99m P280.

Image Evaluation: Both studies 280-32A and 280-32B were open-label, and the protocol called for blinded evaluation of images at the conclusion of the studies, in addition to unblinded reads at the participating institutions. The images for the test agent (Technetium Tc 99m P280) and the 'truth' (contrast venography) were evaluated and interpreted as follows:

The blinded readers were trained using images from other Phase II studies and were instructed on how to grade the images at each region.

According to protocol, the lower bound of the 95% confidence interval for the agreement rate should be at least 60% in order to reject the null. Both studies were designed to enroll at least 105 patients in each study to reject the null hypothesis with 95% power. Assuming 10% non-evaluable patients, the protocol planned to enroll 135 patients for each study.

2.2.2. Results

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2.2.2.1. Patient Accountability

Overall, 280 patients were enrolled under study 280-32. Eleven sites (4 sites in Europe and 7 sites in North America) enrolled 135 patients in study 280-32A and 23 sites (12 sites in Europe and 11 sites in North America) enrolled 145 patients in study 280-32B. The majority of the patients (69% in both studies) were enrolled in North America. Table A shows the patient dispositions in both studies. A total of 37 (13%) of the patients were ineligible for all efficacy evaluations due to protocol violations and failure to complete either Tc 99m P280 imaging or Venography. More patients were unevaluable according to each blinded readers evaluation because they could not determine the diagnosis ranging from 4-6 patients. Patients were also excluded if their CV diagnosis were not made. One hundred and ten patients in study A and 122 patients in study B had all blinded reader evaluations and 'standard of truth'. The sponsor presented results for each blinded readers evaluation compared to standard of truth. Our conclusions are based on the same number of evaluated patients but we also checked the efficacy based on patients evaluable by all readers.

Table A
Patient Accountability in Phase III Efficacy Studies, 280-32A and 280-32B

	STUDY 280-32A (N=135)	STUDY 280-32B (N=145)	Combined (N=280)
Site:			
Europe	34	52	86
North America	101	93	194
Disposition:			
Enrolled	135	145	
Exclusions[1]	17	20	
Efficacy Evaluable (Blind-Read):			
By Reader 1-6[2]			
By All Reader[3]	110	122	232

[1] Excluded due to protocol violations.
[2] Numbers varying between blinded readers evaluation
[3] All patients who were evaluable by all Tc 99m readers and also had CV .

2.2.2.2. Study Independence

The sponsor provided a list of investigators at the participating institutions as well as blinded readers who evaluated Tc 99m P280 images and contrast venography (Appendix 16.1.4, p48-49 for study 280-32A and p334-336 for study 280-32B). None of the investigators in study A participated in study B or vice versa.

The Tc 99m P280 blinded readers (six) in study A also did not participate in the evaluation of images in study B. However, for Contrast Venography, the sponsor listed four individuals (other than readers 1-6) under reader 3 for both studies. Three physicians listed under reader 3 did participate in both studies, thus violating the independent assumptions. There is a possibility that these readers may have introduced bias in evaluating the standard of truth, i.e., diagnosing VT by contrast venography.

2.2.2.3. Patient Characteristics

The majority of the subjects enrolled were caucasian and evenly divided between male and females with a mean age of 60 years , and had onset of signs and symptoms within 10 days shown in Table B. The most commonly reported signs and symptoms of suspected VT were pain and tenderness (85%) followed by swelling (83%). At least 25% of the patients also had a history of DVT or PE and 62% were using heparin followed by other anticoagulation medication.

2.2.2.4. Overall Patient-level Efficacy

Standard of Truth: As per protocol, the primary endpoint was the patient-level agreement rate between Tc 99m P280 and blindly read contrast venography (standard of truth), although the institutional read contrast venography was also used. Table C shows the evaluation of venous thrombosis based on blindly read CV and Tc 99m P280.

There was large variation in diagnosis between studies based on contrast venography than on Tc 99m P280. It appears that CV overdiagnosed VT in study B. There were no explanations regarding this variation between studies.

Note that there were four blinded readers listed under blinded reader 3, of which three readers were common to both studies A and study B, and all three were from Hamilton Civic Hospital Center. The submission did not provide sufficient information on the role played by these readers in determining the standard of truth for studies A and B, which were two months apart.

Table B
Patient Profiles by Studies, Evaluable patients

PATIENT	STUDY 280-32A	STUDY 280-32B	Combined
Demographic Profile:			
Age (yr)			
Mean±SD	59.8±15.8	59.4±15.6	59.6±15.7
Weight (Kg)			
Mean±SD	81.1±18.0	76.1±19.2	78.5±18.7
Gender			
Male	49%	50%	51%
Female	51%	50%	49%
Race			
Caucasian	94%	89%	91%
Black	2%	4%	3%
Others	4%	7%	6%
Clinical Signs & Symptoms[1]:			
Pain/Tenderness	90%	83%	86%
Swelling	85%	82%	83%
Increased Warmth	41%	41%	41%
Erythema	34%	42%	38%
Palpable Cord	8%	9%	8%
Medical History:			
DVT	16%	26%	21%
PE	6%	10%	8%
DVT or PE	20%	28%	24%
Concomitant Medication Use[2]:			
Heparin	58%	65%	62%
Vit. K Antagonists	30%	30%	30%
Anti-platelet	14%	11%	12%
None	32%	27%	30%

[1] Patients with more than one symptoms.
[2] More than one medication.

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Table C
Diagnosis of Acute VT by Blind Read Proceedures, Evaluable Patients.

Proceedure	Study 280-32A			Study 280-32B		
	N*	+	-	N*	+	-
Contrast Venography (Standard of Truth)	114	45%	55%	123	82%	18%
Tc 99m P280:						
Reader 1	113	50%	50%	123	37%	63%
" 2	112	48%	52%	123	28%	72%
" 3	112	44%	56%	123	37%	63%
" 4	113	32%	68%	122	64%	36%
" 5	114	59%	41%	123	52%	48%
" 6	113	42%	58%	123	27%	73%

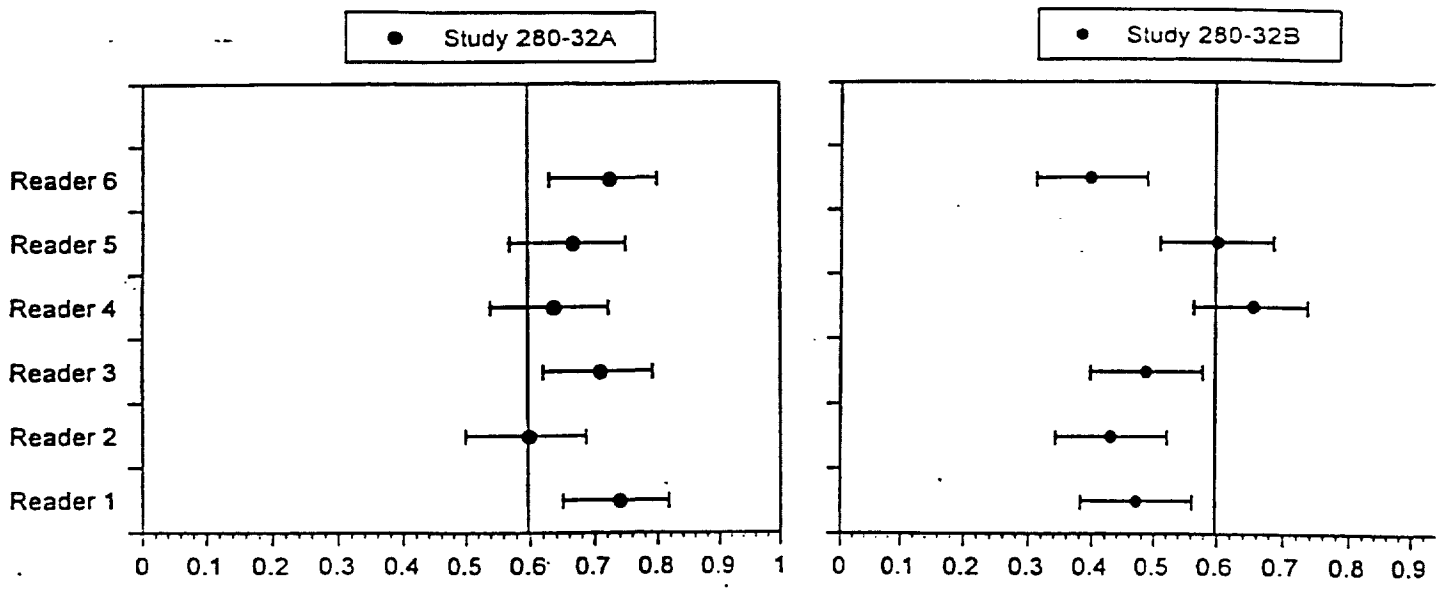
* Excluding patients who had indeterminate results for all regions or who had incomplete venography, negative diagnosis based on less than 2 contiguous negative regions..

Agreement Rate: The patient-level agreement rates and the associated 95% confidence interval, sensitivity and specificity of Technetium Tc 99m P280 with blind and unblind read contrast venography are shown in Table D (Detail Table in Appendix- A, p24-25). The strength of agreement between blinded reader Tc 99m evaluations was poor as measured by *kappa* statistic (, as per reviewers evaluation of pooling both study A and B). A value is considered moderate. The *kappa* values for unblinded reader evaluations were ranging from (a kappa of 0.41 by only one reader) demonstrating that the agreement of Tc 99m P280 with contrast venography was not satisfactory.

Figure 2 depicts the agreement rates and associated 95% confidence intervals by reader and study. As per protocol, the sponsor's goal was to reject the null hypothesis that patient-based agreement rates are less than 60%. If the lower bound of CI includes the point estimate, then the null hypothesis could not be rejected. Individual reader's agreement rates for study A ranged from while for study B ranged from much lower than expected. The null hypothesis could not be rejected according to 3 blinded reader evaluations in study A and the null hypothesis could not be rejected in all blinded readers evaluations in study B. The agreement rate with the unblinded read 'standard of truth', in the lower panel of the figure, demonstrate more consistency between study A and B, though the null hypothesis could still not be rejected as per 5 blindly read evaluations in study B. These results demonstrate that blindly read efficacy of Tc 99m P280 in detecting acute VT could not be substantiated in study B.

'Sample' Sensitivity and Specificity: The 'sample'sensitivity of Tc 99m P280 in study A ranges from and in study B ranges from according to blinded readers evaluation. Based on the unblindly read evaluation, the sensitivity of Tc 99m P280 was also less than or

a) Blindly Read



b) Unblindly Read

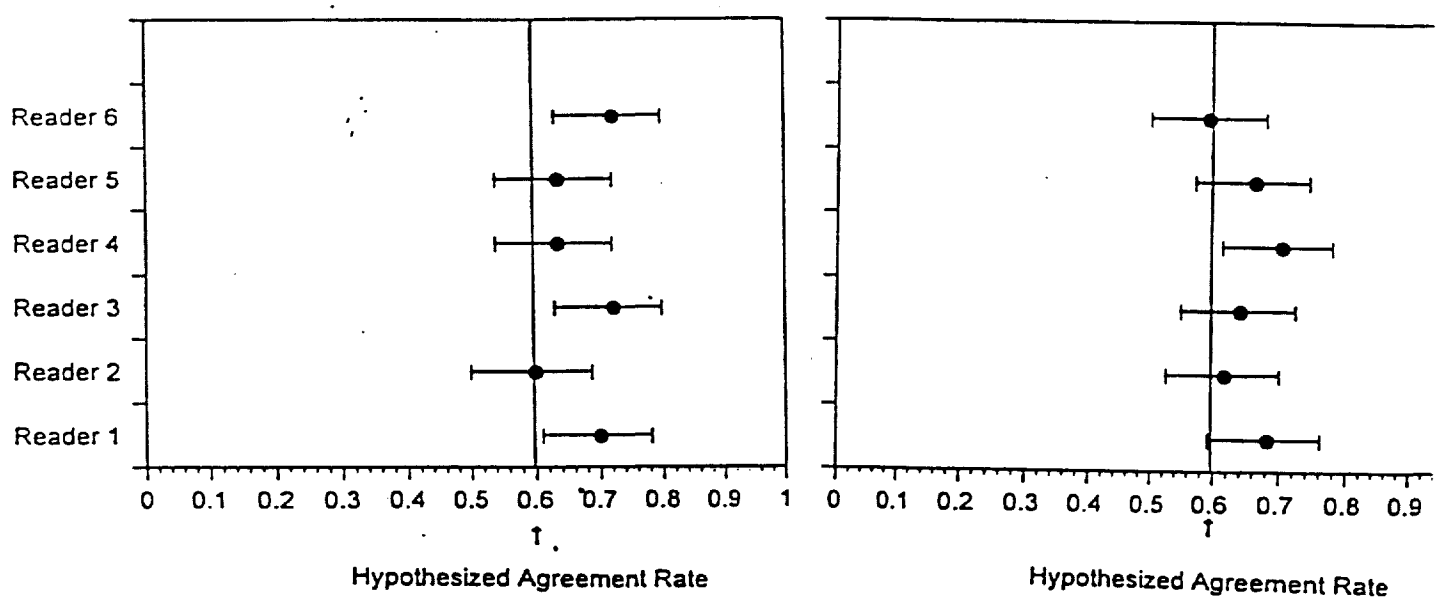


Figure 2: The 95% Confidence Interval for the Agreement Rate of Tc 99m P280 Scintigraphy vs. (a) Blindly Read Contrast Venography, and (b) Unblindly Read Contrast Venography.

equal to 50% according to 3 readers. Therefore, Tc 9m P280 detects more false negatives than false positives assuming the truth, contrast venography, is bias free.

Table D
Agreement Rate, Sensitivity and Specificity of Blind Read Tc 99m P280 vs. Contrast Venography (CV), Evaluable Patients.

Comparator Standard of Truth	Tc 99m Reader	Study 280-32A			Study 280-32B		
		Agreement Rate (95% CI)	Sample Sens.	Sample Spec.	Agreement Rate (95% CI)	Sample Sens.	Sample Spec.
Blinded CV	1	74.3 (65.1 - 81.7)	76.5	73.0	47.2 (38.2 - 56.2)	41.0	77.0
	2	59.8 (50.1 - 68.7)	59.0	61.0	43.1 (34.3 - 52.2)	33.0	91.0
	3	71.4 (62.0 - 79.2)	66.7	75.0	48.8 (39.7 - 57.8)	42.0	82.0
	4	63.7 (54.1 - 72.2)	45.0	79.0	65.6 (56.4 - 73.6)	68.0	54.0
	5	66.7 (57.1 - 75.0)	78.0	57.0	60.2 (51.0 - 68.6)	57.0	73.0
	6	72.6 (63.2 - 80.2)	67.0	77.0	39.8 (31.2 - 48.9)	30.0	86.0
Unblinded CV	1	70.4 (61.1 - 78.2)	79.0	65.0	68.3 (59.2 - 76.1)	56.0	82.0
	2	60.0 (50.4 -68.7)	66.0	56.0	61.8 (52.6 - 70.1)	42.0	84.0
	3	72.2 (62.9 - 79.8)	73.0	72.0	64.2 (55.0 - 72.4)	51.0	79.0
	4	63.5 (53.9 - 72.0)	45.0	75.0	70.5 (61.4 - 78.1)	80.0	60.0
	5	63.5 (53.9 - 72.0)	82.0	52.0	66.4 (57.2 - 74.4)	67.0	66.0
	6	72.2 (63.0 - 79.8)	70.0	73.0	59.3 (60.0 - 76.8)	39.0	82.0

Source: Computed from Tables in Appendix -A

2.2.2.5. Efficacy of Tc 99m P280 *vs.* Ultrasound and Contrast Venography

Study 280-30 enrolled 135 patients to evaluate the agreement rate of Tc 99m P280 with institutional diagnosis of VT using doppler ultrasound (in 126 patients) as the 'standard of truth'. This study was discontinued since ultrasound was not considered a reliable standard of truth for venography. Technetium Tc 99m P280 scintigraphy was evaluated blindly by three independent readers for the presence or absence of VT in each of the nine regions. The standard of truth was evaluated by independent institutional radiologists using patient history, clinical observation, and the confirmatory medical imaging procedure, i.e., ultrasound in most cases but without the knowledge of Tc 99m scintigraphic results.

Although the results of this study were not considered pivotal to support the indication, the study provided an opportunity to compare the agreement between the two 'standards of truth' in detecting VT. Table E shows the agreement rate, sensitivity and specificity based on 3 blind read evaluations of Tc 99m P280 when control standard of truth was ultrasound and contrast venography, respectively. The results demonstrate that even pooled (pivotal studies 280-32A and B) analysis failed to reject the null hypothesis in all blinded reader evaluations of Tc 99m P280 compared to CV. Compared to ultrasound and CV as standard of truth, the agreement rates were similar although the sensitivity was slightly higher for ultrasound. These results do not suggests that one comparator has an edge over the other for detecting acute VT in this patient population.

Table E
Agreement Rate, Sample Sensitivity and Specificity of Blind-Read Tc 99m P280 Compared to Ultrasound and Contrast Venography as 'Standard of Truth'

Reader	Control Standard							
	Ultrasound[1] (Study 280-30)				Blind read Contrast Venography (Study A & B combined)			
	N**	Rate (95% CI)	Sample Sens. (%)	Sample Spec. (%)	N	Rate (95% CI)	Sample Sens. (%)	Sample Spec. (%)
1	112	57.1(47.2 - 66.2)	53.5	69.2	236	60.1(54.0 -.66.2)	52.6	73.8
2	112	54.5(44.8 - 63.7)	51.2	65.4	235	51.0(44.7 - 57.0)	41.4	68.7
3	112	57.1(47.4 - 66.2)	60.5	46.2	235	59.6(53.0 - 66.0)	50.0	77.0

[1] Independent institutional evaluation of Standard of truth based on ultrasound, patient history without knowledge of Tc 99m.
** Evaluable by blinded readers and also had VT diagnosis by Ultrasound.

2.2.2.6. Efficacy of Tc 99m P280 by Imaging time

Three blinded reader's (4, 5, 6) also evaluated Tc 99m P280 images at 10 min., 60 min., and 120-180 min. In response to a question, whether the images at each time point were diagnostic, all readers considered the majority of the images (>90%) to be diagnostic except one reader in study A, who considered only 33% of the images to be diagnostic. The agreement rates at 120-180 minutes window appeared to be lower than at 10 or 60 minutes. But overall, the agreement rates between time points were not statistically significantly different.

2.2.2.7. Efficacy by Subgroups

Chronic *vs.* Acute Thrombosis: To address the concern raised by the clinical reviewer as pointed out in section T.4, we searched for information that should provide evidence that Tc 99m P280 distinguishes between active and chronic VT. In study 280-30, 280-32A and 280-32B, the CRF summarized the patients disease history including whether patients had chronic DVT and or prior histories of DVT or pulmonary embolism (chronic patients) or patients had no documented history of DVT or pulmonary embolism.

The sponsor categorized patients into two distinct subgroups, i.e., acute (no history of DVT or PE) and chronic (history of DVT or PE) and evaluated patient-based agreement rate of Tc 99m P280 with unblinded read contrast venography. Table F shows the agreement rate, sensitivity, and specificity of Tc 99m P280. In both pivotal and non- pivotal studies, the agreements rates in acute patients were statistically significantly ($p<.05$) higher than in chronic patients.

Table F
Agreement Rate, Sample Sensitivity and Specificity of Tc 99m P280 Between Acute and Chronic Patients

Reader	Study 280-30[1] (N=112)				Study A & B Combined[1] (N=237)			
		Rate (%)	Sample Sens.(%)	Sample Spec.(%)		Rate (%)	Sample Sens.(%)	Sample Spec. (%)
1	Acute(n=93)	64.5	63.8	66.7	Acute(n=181)	64.1	57.5	75.0
	Chronic(n=25)	28.0	18.2	100.0	Chronic(n=55)	47.3	38.5	69.0
	p-value	0.00	0.00	0.60	p-value	0.04	0.06	0.84
2	Acute(n=93)	64.0	62.0	71.0	Acute(n=180)	55.0	47.0	68.7
	Chronic(n=25)	24.0	23.0	33.0	Chronic(n=55)	38.0	25.6	68.8
	p-value	0.00	0.00	0.51	p-value	0.04	0.03	0.99
3	Acute(n=93)	64.5	68.0	54.0	Acute(n=180)	63.3	55.8	76.1
	Chronic(n=25)	40.0	45.5	0.0	Chronic(n=55)	47.3	33.3	81.3
	p-value	0.04	0.10	0.24	p-value	0.05	0.03	0.91

[1] In study 280-30, the agreement rate, sensitivity and specificity of Tc 99m P280 was based on ultrasound as standard of truth, while in study 280-32A and B it was based on blind-read contrast venography.

Other Subgroups: Agreement rate of Tc 99m P280 with aggregate (majority results of three readers results) blind-read contrast venography in detecting VT were also evaluated in other major subgroups such as age group (>65 years old vs. <65 years old), gender, duration of signs and symptoms, and concomitant drug use. The percentages of the agreement rates, sensitivity and specificity between subgroups are shown in Table G. There were no statistically significant differences in agreement rates between any subgroups according to both set of blinded reads,

although the rates for males, heparin users, and those who were on vitamin K antagonist were higher. Technetium Tc 99m P280 showed significantly higher sensitivity in detecting VT in heparin users than in non-users.

Table G
Comparison of Agreement Rates, Sensitivity and Specificity using Blinded-Read Contrast Venography as Standard of Truth, Studies 280-32A and B, Evaluable Patients

Subgroups	Read 1			Read 2		
	Agreement Rate	Sens	Specs	Agreement Rate	Sens	Spec
Age:						
<=65 yr (n=132)	59%	45%	77%	61%	49%	75%
> 65 yr(n=103)	56%	51%	73%	73%	70%	81%
Gender:						
Male(n=116)	64%	59%*	73%	68%	67%	71%
Female(n=119)	52%	38%	79%	64%	53%	84%
Ethnicity:						
Caucasian(n=214)	58%	50%	74%	67%	63%*	75%
Others(n=21)	52%	28%	100%	52%	29%	100%
Heparin group:						
Users (n=143)	59%	55%*	74%	69%	66%*	82%
Non-Users(n=92)	56%	25%	77%	61%	39%	75%
Vit. K Antagonist:						
Users (n=70)	61%	57%	83%	70%	69%	77%
Non-User (n=165)	56%	43%	75%	64%	54%	77%
Antiplatelet:						
Users (n=29)	52%	47%	58%	76%	65%	92%
Non-Users(n=206)	59%	48%	79%	65%	59%	75%

Read 1: Aggregate of reader 1, 2, 3; Read 2: aggregate of reader 4, 5, 6.
* Statistically significant ($p<.05$).
Source Table: Appendix - Subgroup.

2.2.3. Comments on Efficacy

The efficacy of Technetium Tc 99m P280 scintigraphy for the detection of VT was evaluated in two Phase III studies 280-32A and B. Both studies followed identical but separate protocols. The primary efficacy endpoint was the agreement rate (detection of positive and negative VT) of Tc 99m P280 with blinded read contrast venography. The two studies enrolled a total of 280 patients suspected of acute VT of which 240 were evaluable for efficacy. The majority of the patients had pain/tenderness or swelling in the limb which are generally the symptoms of thrombophlebitis rather than acute VT. Therefore, it was not clear from the selection criteria whether acute VT patients were adequately represented in Phase III studies. The sponsor did not provide any objective criteria on the CRF such as filling defects or any other features that would presumably be helpful in detecting VT for the blinded reader's grading of positive VT using Tc 99m scintigraphic scans.

Despite these limitations, this review focused on several points: the independence of the studies, the blinded evaluation; the overall efficacy, the efficacy between ultrasound and contrast venography as standard of truth, and efficacy by subgroups.

Both studies 280-32A and B were independent in terms of investigating sites and the blinded read evaluations of Tc 99m P280. But three blinded readers who evaluated the contrast venography as standard of truth in study A also participated in study B. Therefore, they might have introduced bias in detecting VT between the two studies.

The strength of agreement between Tc 99m P280 with contrast venography (kappa ranging from 0.09 to 0.31 as per blinded reader evaluations) was poor. The study A agreement rates, however, were closer to the hypothesized rate (60% or more using the blinded read 'standard of truth') than those for study B. Based on the confidence interval analysis approach specified in the protocol, the null hypothesis could not be rejected according to 3 of 6 blindly read evaluations in study A, and according to all blindly read evaluations in study B. The results using institutional (unblinded) read 'standard of truth' appeared to show higher agreement rates in both studies, but the null hypothesis still could not be rejected according to half of the blinded reader evaluations. Our pooled analysis also failed to reject the null hypothesis in 2 out of 3 blindly read evaluation.

The agreement rates between Tc 99m P280 and the two comparators, ultrasound and contrast venography as control standard were similar. The results do not demonstrate a clear advantage of one standard of truth over the other. Technetium Tc 99m P280 scintigraphy appeared to be more sensitive in acute patients than in chronic patients in both pivotal and non-pivotal studies. However, the criteria used to categorize patients in acute vs. chronic subgroups were loosely defined. The study failed to enroll true positives or true negatives or define some clinical features that would have provided better classification of acute vs. chronic patients. There were no significant differences in agreement rates between other subgroups except that the sensitivity of Tc 99m P280 was significantly higher for heparin users.

The use of 'agreement rate' as an endpoint was not clear and the clinical utility of 60% threshold was not justified.

2.3. SAFETY

This application included safety data from 689 subjects (normal and patients) in eleven Phase I, II, and III studies. Not all studies evaluated vital signs or clinical laboratory tests. In pivotal studies 280-32A and 280-32B, no clinical laboratory assessments were made. The pivotal safety study 280-33 were designed to study both vital signs as well as clinical laboratory measurements in detail. The integrated safety evaluation consists of all patients who were exposed to Technetium Tc 99m P280 and for whom either AE or clinical laboratory measurements were available. In this section, following a description of the pivotal safety trial, our review will include AE profiles of all patients suspected of VT and who were exposed to proposed formulation of Tc 99m P280 and abnormal changes (above the upper limit of the normal range) in hematology, chemistry values, and liver enzyme values.

2.3.1. Description of Phase III Safety Study

Design: Study 280-33 was also a multi center, open-label, within-patient study designed to evaluate the safety of Technetium Tc 99m P280 in patients at risk for VT. Patients, 18 years or older, who were within 10 days of the onset of significant signs and symptoms suggestive of VT or within 10 days following a surgical procedure were eligible for this study.

Each patient was to receive a single intravenous administration of 20 mCi of Tc 99m P280 following pre-study evaluation. Vital signs, hematology, and clinical chemistry values were assessed at 3 and 24 hour post-injection.

Objectives: The *primary* objective of this trial was to assess safety by evaluating pre- and post-injection measurements of hematology, clinical chemistry, urinalysis, vital signs, and incidence of AE's. The *secondary* objective was to assess the agreement rates between the Technetium Tc 99m P280 images and the final institutional diagnosis (unblinded).

Safety Endpoints: Incidence of AE's; clinically significant changes in vital signs and laboratory measurements post-drugs.

Stated Hypothesis and Sample Size: The null hypothesis was that the pre- vs. post mean values for each laboratory measurements were equal. The study was sized with 50 patients to detect a difference of 10% with at least 80% power.

2.3.2. Results

2.3.2.1. Adverse Events

In the three pivotal efficacy and safety studies (study 280-32A and B, and and study 280-33), 34/385(8%) experienced at least one AE. The most frequently experienced event was pain (2.3%) followed by headache (1.0%). Four patients had severe pain that required treatment (study report, vol.1.87, 1.96).

In all Phase II/III studies, a total of 680 patients were exposed to Tc 99m P280 of which 68 were exposed to investigational formulation while 612 were exposed to proposed formulation. The summary of adverse events by body system and by geographic region are shown in Tables G and H in Appendix B. There were a total of 37/680(5%) patients experienced at least one AE. None of the 68 patients exposed to the investigational formulation (not shown in these Tables) experienced any AE

2.3.2.2. Vital Signs

The vital signs were measured up to 3 hours following Tc 99m P280 injection in two efficacy studies 280-32A and 280-32B, and were measured up to 24 hours in safety study 280-33. Summary statistics at baseline and change from baseline to each time points are shown in Appendix C, p27. There were statistically significant decreasing trend in pulse rate and systolic B.P. post-injection in all Phase III studies. But all studies pooled, the decrease at 3 and 24 hours were not significant. The vital sign changes following CV at the same time points post-injection were less pronounced.

The clinically significant changes (Systolic B.P.>35 mmHg, pulse rate>20 beats/min, diastolic B.P.>25 mmHg) in a total of 523 patients studied (all studies combined) were less than 1% at any time points following Tc 99m P280 (vol.1.109, p 51, Integrated safety results).

2.3.2.3. Hematology

Summary of changes from baseline to 3 and 24 hours are shown in Appendix C. There were no significant changes from baseline to post-injection time points for any hematology parameters except for platelet count. The majority of the subjects had hematology values that remained unchanged or shifted from below or above the normal range (Table X, Appendix C).

2.3.2.4. Clinical Chemistry

Clinical chemistry parameters were recorded at baseline and at 3 and 24 hours post-Tc 99m P280 in Phase III safety study 280-33. Summary statistics for selected parameters at each time point post-injection are shown in Appendix C. There were no statistically significant mean differences from baseline to 3 hour or 24 hour post-injection values for any of the chemistry parameters except glucose. Glucose level dropped significantly (p=.04) at 3 hours post-injection but appeared to increase towards baseline level at 24 hours.

In approximately of patients, liver enzymes were elevated above the upper limit of the normal level at 3 and 24 hours post-injection as shown in Table H. However, our examination of the data showed the baseline values for these patients were also above the upper limit of the normal level. Therefore, the suggestion that the drug effects the liver enzymes is inconclusive.

Table H
Summary of Liver Enzymes values above the Upper Limit of the Normal Range, Study 280-33

Parameters		Baseline	3 hour	24 hour
ALT(SGPT) (>50 U/L)	N Mean Range	26 100.0	24 113.0	26 114.0
AST(SGOT) (>55 U/L)	N Mean Range	16 83.0	11 117.0	15 110.0
GGT (>75 U/L)	N Mean Range	36 175.0	34 179.0	35 171.0
Triglycerides (>200 mg/dl)	N Mean Range	26 260.0	26 270.0	19 280.0
Alkaline Phos. (>125 U/L)	N Mean Range	21 206.0	19 208.0	20 203.0

The changes from baseline to 3 hour post-injection in platelets, WBC, and lymphocytes were statistically significant but returned to baseline level at 24 hours. The most clinically significant changes were noted for lymphocytes in 15% of the patients. Only one patient had a clinically significant post-injection hematology value that considered to be related to Tc 99m P280.

3.0. Reviewer's Assessment and Recommendations

The sponsor submitted the results of eleven studies (Phase I, II, III) in which pharmacokinetics, optimal dose, efficacy, and safety of Tc 99m P280 were studied. Three Phase III studies: 280-32A and B, 280-33 were considered pivotal to support the indication that Tc 99m P280 can be used to detect acute Venous Thrombosis (VT). The sponsor claimed that Tc 99m P280 binds to the activated platelets which enables visualization of lesions characterized by activated platelet involvement postulated to be present in recent or active thrombus formation, thereby detecting acute cases. The sponsor also claims that this product has a better safety profile than contrast venography. The *primary efficacy* endpoint was the agreement rate (detection of positive and negative VT) of Tc 99m P280 compared to contrast venography (CV) as 'standard of truth'. Both Tc 99m scintigraphy and CV were evaluated by independent blinded readers. A total of 280 patients were enrolled in both studies A and B following identical but separate protocols, and another 109 patients were enrolled in study 280-33 to study safety profiles.

The objective of the pivotal efficacy studies was to demonstrate that the agreement rate of Tc 99m scintigraphy with CV was at least 60% in detecting acute VT. The sample size of 135 and 145 in study A and B, respectively, were adequate to reject the stated null hypothesis that agreement rate is <60% with sufficient power.

During a Phase III progress meeting with the sponsor, the appropriateness of the agreement rate as primary endpoint was discussed. We raised the concern that although agreement rate is intutively appealing, it does not make any distinction between positive and negative test results. We suggested that in a matched pair design such as in study 280-32, the sensitivity and specificity, and predictive values may have been a better choice of endpoints, provided VT is confirmed. The sponsor insisted on agreement rate as the primary endpoint without giving any scientific rationale to support their point. Lack of an appropriate reference test/standard of truth is a significant drawback in determining the accuracy of a diagnostic test. The use of contrast venography as the standard of truth in the pivotal studies may have induced large bias in the results since it is not an accurate test. Generally, the effect of reference test error bias would likely inflate the test results provided test and reference methods are possibly correlated conditional on true disease status. In addition, the sponsor's decision to use 60% as the cutoff agreement rate for testing the null hypothesis was not justified. Due to these limitations, results based on agreement rate are not likely to show a clear risk-benefit of Tc 99m P280 scintigraphy over contrast venography.

The sponsor also suggested that the unblindly read evaluations should be considered primary. But in an active comparative trial, blindly read evaluation is more appropriate to avoid potential bias. Therefore, this reviewer considers blindly reads to be more appropriate as per protocol.

During the review process, the indication of detecting acute VT was discussed and it appeared that adequate information was needed in order to support the sponsor's claim that Tc 99m P280 can differentiate between phlebitis vs. clots in the limb. Most patients enrolled in both studies

had symptoms such as pain/tenderness and swelling which were indications of *phlebitis*. More than 60% of the patients were also on heparin which is the treatment for thrombosis. The sponsor submitted results for both blinded and unblinded evaluations using evaluable as well as the intent-to-treat subsets. All results were verified using the sponsor's data provided in this submission. Additional analyses were also performed to verify the consistencies in the results.

Based on the results submitted in this application, we can conclude that:

(i) Studies 280-32A and 280-32B were independent with respect to investigator participation and the blinded read of Tc 99m P280 images but may not be independent in terms of standard of truth outcome evaluation since some readers evaluated contrast venography in both studies.

(ii) The strength of agreement between Tc 99m P280 and contrast venography was poor in both study A and B (kappa < 0.40).

(iii) Using the evaluable patient population, there were marginally statistically significant agreements between diagnoses (>60%) according to 3 out of 6 blinded reader evaluations of Tc 99m P280 in study A but there were no statistically significant agreements according to all 6 blinded reader evaluations in study B.

(iv) Using the intent-to-treat population, there was no statistically significant agreement between Tc 99m P280 and contrast venography diagnoses in either study.

(v) The estimated sensitivity for Tc 99m P280 was below 50% according to 4 of 6 blinded readers in study B.

(vi) Technetium Tc 99m P280 appeared to suggest higher sensitivity in acute patients than in chronic patients in both studies combined.

(vii) The estimated sensitivity for Tc 99m P280 was significantly higher in patients in the heparin group compared to the non-heparin group.

(viii) There was evidence of abnormal changes (above the upper limit of normal) in liver enzyme values at post-injection time (up to 24 hours) in patients who also had abnormal values at baseline suggesting that these changes might be attributable to underlying diseases rather than Tc 99m P280.

From a statistical perspective, this reviewer concludes that overall, patient-level efficacy of Tc 99m P280 has not been established in either pivotal trial. Although safety profiles appeared to be satisfactory, the efficacy claims are inadequate to support the indication. Therefore, we recommend that the sponsor provide further evidence that Tc 99m P280 detects acute VT in a well designed study.

/S/

Mahboob Sobhan, Ph.D.
Reviewing Statistician, HFD-720

/S/ 12/6/07

Concur: Michael Welch, Ph.D.

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HFD-720/Drs. Smith, Welch, Sobhan
HFD-160/Hockensmith
HFD-344/B. Barton
HFD-720/File Copy
HFD-720/Chron Copy

APPENDIX - A

AGREEMENT RATE (95% CI) BETWEEN Tc 99m P280 AND CONTRAST VENOGRAPHY, BLIND-READ, EVALUABLE PATIENT, STUDY 280-32A.						
Blinded Reader	No. Evaluable (N)	Tc 99m P280	Contrast Venography		Agreement Rate	95% Confidence Interval
			+	-		
1	113	+	39	17	74.3	65.1 - 81.7
		-	12	45		
2	112	+	30	24	59.8	50.1 - 68.7
		-	21	37		
3	112	+	34	15	71.4	62.0 - 79.2
		-	17	46		
4	113	+	23	13	63.7	54.1 - 72.2
		-	28	49		
5	114	+	40	27	66.7	57.1 - 75.0
		-	11	36		
6	113	+	34	14	72.6	63.2 - 80.2
		-	17	48		
Compiled from Table S51-S57, Table S61-S62, Section 14.2, Vol. 1.89						

AGREEMENT RATE (95% CI) BETWEEN Tc 99m P280 AND CONTRAST VENOGRAPHY, BLIND-READ, EVALUABLE PATIENT, STUDY 280-32B.						
Blinded Reader	No. Evaluable (N)	Tc 99m P280	Contrast Venography		Agreement Rate	95% Confidence Interval
			+	-		
1	123	+	41	5	47.2	38.2 - 56.2
		-	60	17		
2	123	+	33	2	43.1	34.3 - 52.2
		-	68	20		
3	123	+	42	4 .	48.8	39.7 - 57.8
		-	59	18		
4	122	+	68	10	65.6	56.4 - 73.6
		-	32	12		
5	123	+	58	6	60.2	51.0 - 68.6
		-	43	16		
6	123	+	30	3	39.8	31.2 - 48.9
		-	71	19		
Compiled from Table S51-S57, Table S61-S62, Section 14.2, Vol. 1.98						

APPENDIX - B

Table G. A Summary of The Most Commonly[a] Reported Adverse Events
By Body System - All Causality
All Subjects Treated With Technetium Tc 99m P280 In Phase 2/3 Trials
(N=680)

	Number (%) of Subjects			
BODY SYSTEM COSTART Term	Total	Mild	Moderate	Severe
Subjects With at Least One Adverse Event	37 (5)			
BODY				
Pain	10 (1)	3 (<1)	3 (<1)	4 (<1)
Headache	5 (<1)	5 (<1)	0	0
Fever	3 (<1)	3 (<1)	0	0
Asthenia	2 (<1)	0	2 (<1)	0
Pain Back	2 (<1)	2 (<1)	0	0
Pain Chest	2 (<1)	0	1 (<1)	1 (<1)
CARDIOVASCULAR				
Hypotension	2 (<1)	0	2 (<1)	0
DIGESTIVE				
Nausea	4 (<1)	2 (<1)	2 (<1)	0
NERVOUS				
Hypertension	4 (<1)	3 (<1)	1 (<1)	0

a ≥2 subjects
REF: Tables 7.1 and 7.2

Table H. A Summary of The Most Commonly[a] Reported Adverse Events
By Body System and Geographic Region- All Causality
All Subjects Treated With Technetium Tc 99m P280 In Phase 2/3 Trials
(N=680)

	Number (%) of Subjects			
BODY SYSTEM COSTART Term	Total	Europe	Canada	USA
Subjects With at Least One Adverse Event	37/680 (5)	7/119 (6)	15/130 (12)	15/431 (3)
BODY				
Pain	10 (1)	4 (3)	4 (3)	2 (<1)
Headache	5 (<1)	2 (2)	1 (<1)	2 (<1)
Fever	3 (<1)	0	0	3 (<1)
Asthenia	2 (<1)	0	1 (<1)	1 (<1)
Pain Back	2 (<1)	0	0	2 (<1)
Pain Chest	2 (<1)	0	0	2 (<1)
CARDIOVASCULAR				
Hypotension	2 (<1)	1 (<1)	0	1 (<1)
DIGESTIVE				
Nausea	4 (<1)	0	2 (2)	2 (<1)
NERVOUS				
Hypertension	4 (<1)	0	2 (2)	2 (<1)

a ≥2 subjects
REF: Tables 7.8.1 and 7.8.2

APPENDIX - C

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TABLE LXV. SUMMARY OF RESULTS FOR BLOOD PRESSURE AND PULSE RATE, STUDY 280-32A

		Technetium Tc 99m P280				Contrast Venography			
Time	Parameter	N	Mean	Std. Dev.	P Sign Rank	N	Mean	Std. Dev.	P Sign Rar
Baseline	Systolic B.P.	132	136.2	19.9		92	136.3	20.7	
	Diastolic B.P.	132	77.0	10.5		92	77.9	11.2	
10 Min Change	Systolic B.P.	130	-1.7	10.3	0.022	65	0.9	14.3	0.690
	Diastolic B.P.	130	-0.5	5.8	0.171	64	-2.2	7.5	0.004
30 Min Change	Systolic B.P.	130	-3.3	10.4	<0.001	62	-3.1	14.1	0.051
	Diastolic B.P.	130	-0.9	6.5	0.060	62	-1.4	6.8	0.078
90 Min Change	Systolic B.P.	127	-2.1	11.0	0.021	35	-1.9	14.9	0.474
	Diastolic B.P.	127	-0.9	6.7	0.080	35	-0.8	9.2	0.542
180 Min Change	Systolic B.P.	115	-3.2	11.8	<0.001	22	-2.2	19.4	0.389
	Diastolic B.P.	115	-0.8	6.6	0.090	22	1.5	9.8	0.620
Baseline	Pulse Rate	133	77.2	13.2		96	79.0	12.9	
10 Min Change	Pulse Rate	131	-1.4	5.7	0.012	71	-2.2	8.0	0.006
30 Min Change	Pulse Rate	131	-2.9	6.3	<0.001	64	-2.5	9.0	0.006
90 Min Change	Pulse Rate	128	-3.2	7.8	<0.001	36	-3.2	9.5	0.038
180 Min Change	Pulse Rate	116	-3.3	8.6	<0.001	22	-2.1	12.6	0.660

BEST POSSIBLE

TABLE LXIV. SUMMARY OF RESULTS FOR BLOOD PRESSURE AND PULSE RATE, STUDY 280-32B

		Technetium Tc 99m P280				Contrast Venography			
Parameter	Time	N	Mean	Std. Dev.	P Sign Rank	N	Mean	Std. Dev.	P Sign Rank
Systolic B.P. (mmHg)	Baseline	142	131.9	20.3		93	135.8	22.2	
	10 Min Change	138	0.0	10.1	0.684	68	0.8	9.5	0.819
	30 Min Change	140	-1.6	12.7	0.117	70	-1.3	14.9	0.404
	90 Min Change	136	-0.7	12.1	0.595	55	-2.4	13.0	0.171
	180 Min Change	130	2.5	13.7	0.030	55	-3.5	14.7	0.117
Diastolic B.P. (mmHg)	Baseline	142	76.2	14.2		92	77.5	11.9	
	10 Min Change	138	0.0	7.6	0.713	67	0.2	7.0	0.759
	30 Min Change	140	0.3	10.3	0.898	69	-1.3	9.9	0.281
	90 Min Change	136	0.7	10.3	0.458	54	-1.3	8.3	0.113
	180 Min Change	130	2.2	10.6	0.056	54	-2.4	11.0	0.219
Pulse (bpm)	Baseline	142	78.7	12.4		93	81.3	14.1	
	10 Min Change	138	-2.3	6.3	<0.001	68	-0.4	8.9	0.661
	30 Min Change	140	-3.1	7.4	<0.001	70	-3.1	11.1	0.016
	90 Min Change	136	-3.1	7.8	<0.001	56	-2.8	9.8	0.016
	180 Min Change	130	-2.6	7.5	<0.001	55	-0.5	11.1	0.623

Summary of Vital Signs, Study 280-33, Evaluable Patients (n=107)							
Parameter		Baseline	5 min	30 min	60 min	3 hour	24 hour
Systolic B.P.	Mean + SD Change P-value	133 ±20.6	132 ± 20.7 -0.2 NS	133 ±20.4 0 NS	132 ±20.5 -0.3 NS	133 ±17.6 0.4 NS	132 ± 18.2 0.2 NS
Diastolic B.P.	Mean + SD Change P-value	77 ± 11.6	78 ± 12.0 0.7 NS	77 ± 11.7 0.6 NS	77 ±11.1 0.4 NS	76 ± 10.6 -0.4 NS	75 ±10.1 -1.5 NS
Pulse Rate	Mean + SD Change P-value	80 ± 16.3	79 ± 16.6 -0.6 NS	78 ± 16.4 -1.8 0.00	78 ± 16.1 -1.9 0.00	79 ± 16.0 -0.9 0.20	79 ± 16.0 -1.4 0.04

Summary of Results for Clinical Chemistry, Study 280-33(n=107)				
Parameter		Baseline	3 hour	24 hour
ALT/SGPT	Mean + SD Change p-value	40.5 ±54.2	42.8 ±58.5 2.0 NS	45.2 ± 63.0 4.0 NS
AST/SGOT	Mean + SD Change p-value	33.7 ± 25.5	35.2 ± 44.0 2.7	36.2 ±42.4 2.0
Albumin	Mean + SD Change p-value	3.5 ±0.7	3.5 ± 0.7 0.0 NS	3.5 ± 0.7 0.0 NS
BUN	Mean + SD Change p-value	16.4 ±8.0	16.7 ± 8.6 -0.3 NS	17.2 ± 7.9 -0.5 0.09
GGT	Mean + SD Change p-value	78.7 ± 93.5	80.3 ± 96.0 -0.8 NS	79.7 ±98.3 -2.5 0.37
Glucose	Mean + SD Change p-value	134.4 ± 88.0	118.1 ± 40.4 10.2 0.04	129.2 ± 59.2 4.8 0.74
Direct Bilirubin	Mean + SD Change p-value	0.14 ± 0.25	0.16 ± 0.26 0.11	0.16 ± 0.30 0.00

Summary of Results for Hematology Values, Study 280-33(n=107)				
Parameter		Baseline	3 hour	24 hour
Platelets	Mean + SD Change p-value	267 ±135.0	274 ±138.0 5.1 0.01	271 ± 108.0 11.3 0.00
Hematocrit	Mean + SD Change p-value	37 ± 6.3	37 ±6.1 0.2 NS	37 ±6.5 0.1 NS
Hemoglobin	Mean + SD Change p-value	12.4 ±2.1	12.5 ±2.1 0.0 NS	12.4 ±2.2 0.0 NS
Lymphocytes	Mean + SD Change p-value	20.4 ±10.0	21.5 ±10.3 1.0 0.02	21.4 ±10.0 0.8 0.13
RBC	Mean + SD Change p-value	4.0 ± 0.7	4.1 ±0.6 0.00 NS	4.0 ± 0.7 0.00 NS
WBC	Mean + SD Change p-value	8.9 ±4.0	9.2 ±4.1 0.3 0.00	8.7 ±3.8 0.2 0.27

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020887

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-160
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

NOV 20 1997

Microbiologist's Review #1 of NDA 20-887/BI
November 13, 1997

A. 1. **APPLICATION NUMBER:** 20-887/BI

APPLICANT: Diatide, Inc.
9 Delta Drive
Londonderry, New Hampshire 03053

2. **PRODUCT NAMES:** Kit for the Preparation of Technetium Tc 99m Apcitide

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** The drug product is packaged in lyophilized vial containing 100 ug peptide. It is to be administered intravenously with approximately 20 mCi of technetium-99m.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Detection and localization of acute venous thrombosis

B. 1. **DATE OF INITIAL SUBMISSION:** August 19, 1997

2. **AMENDMENT:** November 7, 1997

3. **RELATED DOCUMENTS:**

4. **ASSIGNED FOR REVIEW:** November 13, 1997

5. **DATE OF CONSULT REQUEST:** November 12, 1997

C. **REMARKS:**

The submission responds to questions presented to the applicant as a result of Microbiologist's Review #1.

D. CONCLUSIONS:

Satisfactory responses were made by the Applicant. The submission is recommended for approval with respect to microbiology.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

/S/ 11/13/97

Brenda Uratani, Ph.D.
Review Microbiologist

APPEARS THIS WAY
ON ORIGINAL

/S/ - 11/20/97

APPEARS THIS WAY
ON ORIGINAL

cc:

NDA 20-887
HFD-160/ Div. File
HFD-805/ Uratani
HFD-160/CSO/ Hockensmith
drafted by: Brenda Uratani, 11/13/97
R/D initialed by P. Cooney, 11/13/97

REVIEW FOR HFD-160
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review #1 of NDA 20-887
October 3, 1997

A. 1. **APPLICATION NUMBER:** 20-887

APPLICANT: Diatide, Inc.
9 Delta Drive
Londonderry, New Hampshire 03053

2. **PRODUCT NAMES:** Kit for the Preparation of Technetium Tc 99m Apcitide

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** The drug product is packaged in lyophilized vial containing 100 ug peptide. It is to be administered intravenously with approximately 20 mCi of technetium-99m.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Detection and localization of acute venous thrombosis

B. 1. **DATE OF INITIAL SUBMISSION:** August 19, 1997

2. **AMENDMENT:** none

3. **RELATED DOCUMENTS:**

4. **ASSIGNED FOR REVIEW:** August 26, 1997

5. **DATE OF CONSULT REQUEST:** August 26, 1997

C. **REMARKS:**

Technetium Tc 99m apcitide binds to platelets on acute thrombi allowing detection of the thrombi by gamma camera imaging. Bibapcitide, a symmetrical dimer of the 13 amino acid peptide apcitide, binds to the glycoprotein IIb/IIIa receptor of human platelets.

D. CONCLUSIONS:

The submission is not recommended for approval as submitted.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

/S/ 10/3/97

Brenda Uratani, Ph.D.
Review Microbiologist

APPEARS THIS WAY
ON ORIGINAL

/S/ 10/3/97

APPEARS THIS WAY
ON ORIGINAL

cc:

NDA 20-887
HFD-160/ Div. File
HFD-805/ Uratani
HFD-/CSO/ Hockensmith
drafted by: Brenda Uratani, 10/3/97
R/D initialed by P. Cooney, 10/3/97