

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020887**

**MEDICAL REVIEW(S)**

DEC 10 1997

Medical Officer Review

NDA# 20887  
M.O. Review # 1

Date of letter: 8/24/97  
Date FDA received: 8/25/97  
Date reviewer received: 9/3/97  
Date review completed: 12/8/97

1. General Information

Drug name: <sup>99m</sup>Tc Apcitide  
Generic name:  
Proposed trade name: AcuTect  
Chemical name: <sup>99m</sup>Tc-P280 (peptide) Injection  
Status: Priority submission

Sponsor: Diatech, Inc.  
9 Delta Drive  
Londonderry NH 63053

Pharmacologic Category: Diagnostic radiopharmaceutical

Proposed Indication(s): Detection and localization of acute venous thrombosis

Dosage Form(s) and  
Route(s) of Administration,  
Directions for Use: "20 mCi in a solution containing 100ug  
P280 peptide.",  
intravenously,  
specific activity not specified

NA Drug Classification:

Related Drugs: None

Related Reviews: Statistical Review : Mahboob Sobhan, Ph.D.  
Biopharm dated: David Udo, Ph.D.  
Chemistry Review dated: Qansy Salako, Ph.D.  
Pharmacology/Toxicology Review: Adebayo Lanionyu, Ph.D.

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Note: All the statements made by Sponsor in the submission, which appear in this review, are in italics. These were transferred from the submission ad verbatim. All the appendices are as they appeared in the submission.

3. Material Reviewed

Clinical data appears in volumes 27 - 71 and was reviewed in full.

4. Chemistry/Manufacturing Controls

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Please refer also to the Chemistry Review of this submission.

As the Sponsor proceeded with the development of this drug product, its answers to questions about the drug composition always implied the existence of only a single drug substance in terms of molecular structure. Two identical peptide chains were supposed to be linked by the radioactive Technetium molecule.

The sponsor claims that the change in understanding of chemistry of the drug has nothing to do with its diagnostic clinical value and its clinical impact. It should be pointed out that from the outset of the clinical development, various aspects of the formula have been changed numerous times. However, no evidence is presented in this submission on the comparative chemical, pharmacologic or clinical properties of various formulations.

The final drug formulation is supposed to be metabolized into two components, but none of these parts has been characterized. It is also unknown what the relationship of the metabolites is to any of the original 2 or 3 components.

5. Animal Pharmacology/Toxicology

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Please refer also to the Pharmacology/ Toxicology Review of this submission.

As it will become apparent, from the review of evidence presented in this submission, the scientific basis for the use of this drug to image thrombi is not firm and may be dubious. Although the Sponsor claims that a receptor is involved, there is no evidence to suggest that this actually happens when the drug is injected clinically. The preclinical use of the drug involved a surgical procedure along with other manipulations, which is not a good model which were taken to substitute for the pathologic clot (thrombus). This was inappropriate as 1) activation of platelets occurs in surgical injury and inflammation at the site, and 2) nonspecific uptake will occur at the site of venous trauma or surgery.

Clinically, there are at least four different reasons why it is unlikely that a substantial uptake of the radiopharmaceutical at the site of forming thrombus can be observed based on the current knowledge. 1) The site of attachment to which the radiopharmaceutical is to adhere on activated platelets is the same as that for fibrinogen, fibronectin and von Vellebrand factor. At least, the concentration of fibrinogen is 10,000 greater than that of the peptide radiopharmaceutical. 2) The affinity of fibrinogen to the site is about 100 times greater than that of the radiopharmaceutical according to the earlier literature cited by the Sponsor. 3) The radiopharmaceutical is of a relatively low specific activity. 4) The radiopharmaceutical contains an undetermined proportion of unlabeled peptide along with other similar peptides which compete with the labeled peptide for the site already occupied by the avid and more numerous fibrinogen molecules.

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As a part of this NDA, the Sponsor submitted additional information on the drug product and it appears that it differs substantially from the compound in the articles referenced. However, although the binding affinity of the compound now used to the activated platelets may be somewhat higher, or, at least, different from the one cited in the literature and in the earlier submissions, the current formula has not been characterized sufficiently so that the mechanism of its clinical action may be described clearly and convincingly. That is to say that the peptide sequence is not exclusive or unique by any stretch of imagination, as similar peptides can be found as a part of a family of protein receptors called integrins. In addition, testing of crossreactivity with endogenous proteins and peptides not only in animals, but preferably in a pertinent clinical setting should be performed to bear on potential efficacy as well as safety.

In addition, there are numerous disease conditions, most notably inflammation and neoplasia, where prominent activation of platelets occurs. There are also diseases characterized by abnormal levels of fibrinogen such as glomerulonephritis, various fibrinogen deficiencies as well as fibrinogen level fluctuations such as that seen in acute phase reactions, which may substantially alter the results.

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## 6. Clinical Background

Venous thrombosis is an infrequent condition in the healthy, young population, but its frequency increases with age. High risk of venous thrombosis is associated with severe burns or other forms of trauma, postoperative and postpartum states, disseminated cancer, nephrotic syndrome and all serious illnesses and prolonged bed rest. High incidence of thrombosis is with cardiac disease such as congestive heart failure, myocardial infarction and rheumatic heart disease. Phlebothrombosis is known to be associated with cancer and there is also some relationship to the use of oral contraceptives particularly those with high estrogen content.

Venous thrombosis requires treatment with heparin or warfarin, which have unwanted side effects, and therefore, its diagnosis requires a sufficient degree of accuracy. On the other hand, a related condition, superficial thrombophlebitis requires no specific treatment beside, perhaps, some antiinflammatory drugs which have much milder side effects.

Those are the practical reasons why the two conditions, superficial thrombophlebitis and deep venous thrombosis, should be distinguished, while it should be recognized that there is a tendency on part of some physicians to use the terms interchangeably. Although venous thrombosis may progress towards a combination with thrombophlebitis, there is a considerable risk in overdiagnosing superficial thrombophlebitis as venous thrombosis, since the patient may be exposed to the treatment which may not only be unnecessary, but also potentially harmful by increasing the risk for gastrointestinal hemorrhage, hematoma, hematuria, retroperitoneal bleeding, thrombocytopenia, etc.

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#### 6.1 Relevant Human Experience

In the protocol for the pivotal Phase 3 study the Sponsor listed as its objective: "*To evaluate <sup>99m</sup>Tc-P280 for its ability to detect and localize venous thrombosis by gamma scintigraphy, using contrast venography as the standard.*"

Venous thrombosis has been always a difficult clinical diagnosis to make as, on the one hand, many venous thrombi may never be detected clinically and, on the other, thrombi are not always present when signs and symptoms suggesting their presence are noted. In addition, reliable standards with which to compare a potential new diagnostic procedure are few and most have only a limited use when more than one anatomic location is considered. Thus, for example, impedance plethysmography is usable proximally to the iliac vein, but not for the calf.

The Sponsor chose contrast venography as the standard to verify the presence of venous thrombosis, but as the pivotal trials show, the blinded readers were inconsistent in their results and majority rule blind read or an unacceptable consensus read was resorted to when a standard of truth was obtained. This deviation from the protocol has its methodological and statistical implications in which the deviation from the protocol is only the first hindrance. One of the other implications is that the complexity of obtaining the true diagnosis requires multiple steps. Whether the Sponsor succeeded in that effort is open to questions as no other methods except for contrast venography were attempted in the pivotal study.

One of the main aspects which requires special consideration in thrombus imaging is the differentiation between deep venous thrombosis and superficial thrombophlebitis and presents a methodological dilemma particularly since there is no need to image superficial thrombophlebitis. Taking into the account the fact that the symptoms such as redness, hyperemia, tenderness and to some extent also pain are frequently associated with the superficial thrombophlebitis, there are only a limited number of symptoms one can utilize to select patients with deep venous thrombosis. Perhaps only Homan's sign is more typical for patients with deep venous thrombosis than superficial thrombophlebitis.. Patients were not included in this study based on Homan's sign only, but rather on all the symptoms mentioned above for superficial thrombophlebitis. Thus, the blind read of scintigraphy should have attempted to separate the cases of deep venous thrombosis and superficial thrombophlebitis. However, the positive and negative scintigraphy results were read. All positives were supposedly considered to be evidence for thrombosis.

Stratification of patients based on presenting signs and symptoms could have been helpful to distinguish between deep venous thrombosis and superficial thrombophlebitis. In not doing so a clear scintigraphic presentation of superficial thrombophlebitis cannot be depicted with any degree of certainty. The Sponsor did not attempt to apply this reasoning in the image interpretation. Retrospectively, it is difficult to determine whether the Acutest methodology can differentiate between deep venous thrombosis and superficial thrombophlebitis. Likewise, it cannot be determined with certainty whether what is called thrombus is not actually a case of thrombophlebitis, or, for that matter, what proportion of cases called deep venous thrombosis are actually that and which proportion are truly the patients with superficial thrombophlebitis.

From a nuclear medicine physician-reader's perspective, the interpretation of scintigraphy results require electronic enhancement procedure to subtract background activity. In addition, the two imaging procedures used in the pivotal trials utilize different features to determine whether an image is positive for thrombosis. Cutoffs and filling defects are presumably used on contrast venography. For the scintigraphy to be called positive no cutoffs are sought, but, according to the Sponsor positive findings are largely called "*linear lesions*" when present in two contiguous fields (e.g. thigh-knee, knee-calf, etc.), which means that their length must exceed several inches. These lesions in majority of instances are "hot spots", not the filling defects which would presumably be "cold". The earlier this is seen after the drug injection, the more surprising this is would be. As the Sponsor generally did not find much of a difference in images taken at 10 min, 60 min and 120 min it is questionable whether these areas of uptake represent areas of thrombus. Thus, it may be, that the visualization of long areas of "linear uptake" are likely to be evidence of nonspecific uptake or inflammation rather than thrombus is being formed. Since the same or similar receptor to that seen

on activated platelets is also known to be present on endothelial cells, the linear uptake may also present with endothelial inflammation, otherwise altered endothelium or perhaps even when changes of endothelium are not apparent anatomically.

## 6.2 Important Information from related INDs and NDAs

None.

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## 6.3 Foreign Experience

There is no earlier foreign experience.

## 6.4 Human Pharmacology, pharmacokinetics, pharmacodynamics

Please refer to the Biopharmaceutics Review.

## 6.5 Other relevant background information

None.

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## 7. Description of Clinical Data Sources

### 8. Clinical Studies

The reviewer examined the Sponsor's trials to find answers to hypotheses looking for evidence to support the applicant's claims.

#### 8.1 Reviewer's Trial # I Sponsor's protocol 280 - 32A

##### 8.1.1 Sponsor stated Objective

In the protocol for the pivotal Phase 3 study the Sponsor's objective was: *"To evaluate <sup>99m</sup>Tc-P280 for its ability to detect and localize venous thrombosis by gamma scintigraphy, using contrast venography as the standard."*

Venous thrombosis is mainly recognized as a frequent cause of pulmonary embolism. In conjunction with an inflammation of the venous wall it is referred to as thrombophlebitis. Perhaps even deep venous thrombophlebitis needs to be distinguished from superficial thrombophlebitis since the superficial thrombophlebitis exhibits overt signs and symptoms, but otherwise it is relatively harmless.

Deep venous thrombosis is frequently asymptomatic and becomes suspect at the time of pulmonary embolism. Therefore, the onset of venous thrombosis is not suspected except for an underlying conditions resulting in venous stasis, injury to the venous wall, hypercoaguable state or their combination.

A noninvasive procedure for the diagnosis of venous thrombosis at its outset would be of considerable help not only when the disease is localized in the legs, but it could potentially proven useful in orthopedic patients particularly the elderly, neurosurgery patients and the patients with various heart conditions as the thrombotic process in conjunction with atherosclerosis contributes to a large extent to the clinical presentation of myocardial infarction. In addition, if useful in the heart, the prospective agent could potentially be used to monitor the potential acute recurrence of disease following urokinase, streptokinase or PTCA treatment.

The mechanism of thrombus formation is well described in specialized literature, but it is an orderly sequence, a pathway, in which some steps are only of very short duration (seconds or minutes). In other words, the thrombus generation is not a continuous process, and particularly the initial stages of the pathway are only of a very short duration:

Consequently, to devise and test a useful tool for the diagnosis of venous thrombosis is a daunting task, which is everything but simple.

### 8.1.2 Design

The pivotal study was originally designed as two prospective, open end, multicenter, single dose trials. At the end a blind read was planned with contrast venography as a comparator. Following imaging at 10 min, 60 min and 120 min post-injection the scintigraphy study was to be blindly read and was to be considered "... *positive if there is focal uptake in the vasculature that is greater than either the corresponding contralateral region or surrounding ipsilateral regions or focal uptake that intensifies with time. ...*" (Vol.1.27, p.000006, par.2). Only later was the Supplemental Case Report Form (Appendix O) devised to provide for implementation of "Blind Read Criteria", which did not center on the focal uptake (Appendix K).

The following anatomic areas were to be separately evaluated: right calf, right knee, right thigh, right iliac, left calf, left knee, left thigh, left iliac and inferior vena cava.

### 8.1.3 Protocol

By way of introduction it may be relevant to point out that the sponsor did solicit comments from the FDA in the course of the development of this drug, but that was done mostly after the Sponsor had initiated the respective trials. Only for the last large safety trial and the PK trial were the comments from the Agency provided beforehand.

It is unfortunate that in Phase 2 and Phase 3 open communication was not established between the Sponsor and the Division.

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Thus, for example, by the time the Phase 3 was in progress the sponsor had not 1) yet submitted the CRFs to be used for recording the efficacy readings; 2) made provisions for entry into the study of all patients suspected of thrombosis (which may or may not have similar signs and symptoms as in case of trauma, inflammation, cyst, etc.); 3) determined the optimal dose; 4) studied metabolism of the drug and supplied basic information about metabolites; 5) determined the degree of immunogenicity of the drug or its metabolites and had not provided documentation of methodologies of the procedure to measure antibodies and/or immune complexes; 6) initiated placebo comparisons; 7) provided other essential information about the drug, reasoning that it would have been added at the time the NDA submission. This was unfortunate as all these considerations should have been settled before the Phase 3 study had proceeded.

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A safety issue is the question of antibodies directed against the injected drug and its metabolites, as foreign proteins, and related circulating immune complexes. Their existence has to be presumed until proven otherwise. If present, antibodies could have potentially disastrous consequences on kidney and renal function, as well as a number of other organs.

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The sponsor had referred to a desirable outcome of the procedure as a focal uptake in the vasculature. This was a significant departure from what the sponsor had presented at one of the earlier meetings. There a significant discussion centered on this point since among a number of films shown by the sponsor only 1 or 2 showed a discernible focal accumulation. The representatives of the sponsor believed that merely visualization of vessels meant a positive outcome, namely, phlebitis. However, it is important clinically that thrombosis and phlebitis be distinguished since they indicate a different disease process with potentially different therapeutic implications.

The timing of imaging was in doubt since the schedules for the proposed Phase 2 and Phase 3 differed from one another. Since only one imaging time was proposed for Phase 2 and the use of variable doses of the radiopharmaceutical was planned, the question of optimal time for imaging was open beyond the Phase 2 experiment.

At the time FDA urged that the sponsor to establish and validate an assay for measuring immune complexes and antibodies directed against the radiopharmaceutical and/or its metabolites. Each patient, before receiving the drug should have had a titer established and those with high titer should have been scrutinized further to assess its relationship to the patient's safety profile (even from a long-term perspective).

In addition, it was considered unacceptable for the sponsor to ignore the results of pre-clinical 14-day studies with the radiopharmaceutical in rats and in rabbits which showed significant effect on weight of several organs in both instances and dismiss them as follows: (for rats) *"Statistically significant weight differences in the hearts, kidneys, lungs, ovaries and thyroids were observed in the test groups when compared to the saline control group, but were considered to be incidental..."*

*"(Investigator's Brochure, p.5-29, par.1, line 6) and (for rabbits) "Statistically significant weight differences in the kidneys, spleens and testes were observed in the test groups when compared to the saline group, but were considered incidental..."(Investigator's Brochure, p.5-29, par.4, line 7). Not surprisingly, a likely edema as a result of injury and the starting sign of the pathology of the kidneys resulted in both instances.*

In reference to data interpretation the following was then noted: *"Study will be considered positive if there is focal uptake in the vasculature that is greater than either similar contralateral regions, or surrounding ipsilateral regions. Any non-vascular lesions that are detected will be noted."* This was compared with CRF: *"...presence of vascular or nonvascular uptake..."* was sought as evidence of efficacy.

In summary, at the start of the Phase 3 study there were aspects of the development of this radiopharmaceutical which the sponsor had not addressed. There was little evidence that the drug worked as projected and remaining questions on both safety and efficacy of the drug minimized the potential contribution FDA might have had to the development plan.

#### 8.1.3.1 Population.

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##### *Inclusion Criteria*

- *"significant signs and symptoms suggestive of venous thrombosis" within the last 10 days;*
- *10 days following a surgical procedure that is associated with high risk for development of venous thrombosis;*

*Subject of either sex at least 18 years old.*

### Exclusion Criteria

- pregnancy or breast feeding
- patient unable to remain quietly supine
- another investigational drug within 30 days
- unwillingness to have contrast venogram;

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#### 8.1.3.2 Efficacy endpoint outcomes.

Patients with signs/symptoms of venous thrombosis and those post-surgery underwent SPECT radionuclide scintigraphy following intravenous injection with <sup>99m</sup>Tc-P280 and the results were compared with the respective studies using contrast venography. The signs and symptoms of venous thrombosis were not spelled out in the protocol nor in the Investigator's brochure. The patient selection which could have had a decisive impact on the study results was left to the interpretation of patient conditions by no less than 34 different clinical investigators. Likewise, the "...surgical procedures.. associated with high risk for development of venous thrombosis" were not spelled out.

SPECT images were collected at three different times (10 min, 60 min and 120 min).

Initially the Sponsor's approach to interpretation of the study results was : *"Study will be considered positive if there is focal uptake in the vasculature that is greater than either similar contralateral regions, or surrounding ipsilateral regions. Any non-vascular lesions that are detected will be noted."* It was also referred to in CRF as: *"...presence of vascular or nonvascular uptake..."*.

A blind read of data was performed. The instructions to the blinded readers did not list the focal uptake in the vasculature (Appendix K).

The contrast venography to be used for comparison was not described in detail, including the contrast agent and what would be the standard criteria to evaluate the results.

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#### 8.1.3.3 Statistical considerations

Please refer to the Statistical Review. The numerical treatment of efficacy data is not performed in this review as the Biometrics received the data in a format conducive to computerized data processing. Otherwise, the efficacy issues will be commented upon throughout this review, as necessary.

#### 8.1.3.4 Safety considerations

In the pivotal trials the safety follow-up was limited to recording vital signs and adverse drug events.

The required information about the main metabolites was not obtained in advance and nor was the data to assess immunogenicity.

#### 8.1.4 Results

##### 8.1.4.1.1 Population enrolled

The patient population in this trial included 135 subjects in 11 centers in the US, Canada, England and Belgium. (Appendix A, Table IV). A segment of these patients had a history of PE and DVT (Appendix B). As it turns, contrast venography was positive in 44.7% of this patient sample (Appendix C). Most of these patients had a recent onset of symptoms or surgery (Appendix D) and pain/tenderness/ Homan sign was absent only in 6.8% of cases (Appendix E).

##### 8.1.4.1.2 Efficacy endpoint outcomes

The Sponsor enrolled 135 patients in the first pivotal study and "*imaging was not completed*" on 7 of the 135. Either an injection was not given or a procedure was not performed after the injection. One patient was said to be too uncomfortable to perform the test. Two other patients were "ineligible" (Vol.45, p.62, Table V,) for analysis because signs and symptoms had lasted more than 10 days.

The Sponsor also excluded as "ineligible for efficacy" 8 patients who received (Vol.45, p.62) less than 70 ug dose. Furthermore, 1 patient was excluded from analysis for efficacy because a dose less than 10 mCi. These 9 exclusions leave 117 patients eligible for analysis.

Also the Sponsor did not include another 16 patients considered as "*data not evaluable based on efficacy results*" (Vol.45, p.65, Table VII) for various reasons such as an "indeterminate" call on blind read venography or venography results not available, which is unacceptable because it is irrelevant in comparing the blind read assessments. This brings the total of evaluable patients, after the Sponsor's exclusions, to 101.

It is unacceptable to list the number of Evaluable patients as larger than 101 in various sections of the submission such as 114 (Vol.45, p. 84, Table XXIII). The use of results calculated per intent-to-treat patients such as 131 (Vol.45, p.87, Table XXV) provides

limited information since in many instances only a very depleted data set per patient is available. The Sponsor tended to bring into the main analysis and sub-analyses of efficacy, data from patients once pronounced ineligible and unevaluable. This makes an analysis uninterpretable and the issue of efficacy confusing.

The diagnostic agreement between contrast venography and scintigraphic imaging with Acutect was the primary efficacy variable as evident from the Integrated Summary of Effectiveness (Vol.23, 808299, par.5). The primary efficacy data can be found in Volumes 1.46-48.

#### 8.1.4.1.3 Safety outcomes

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##### Adverse Drug Events

The time period for observing and reporting ADEs was not specified in the protocol, otherwise, the descriptions of ADEs as well as the Case Report Form are adequate. The latest ADEs reported in this submission had the onset at 100 min and the longest duration of an ADE was 360 min. It is unlikely that observation and reporting went beyond these time periods, but the time period covered by the individual investigators is unknown.

The sponsor reported a total of 7 ADEs in 4 subjects out of 135 patients. Thus, the proportion is about 3% in this trial, The Sponsor considered all the ADEs as probably unrelated to drug. Three of them were considered mild, three moderate and 1 severe. The severe ADE was described as a pain starting 60 min after the injection and lasting 59 min.(Vol. 32, p.000134, Table LXIII). Moderate ADEs were hypotension, pallor and sweat all in one patient which were considered clinically significant. There were also 2 cases of mild headache and 1 case of mild pain.

##### Vital signs

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Vital signs were collected at baseline and at 10 min, 30 min, 90 min and 180 min, post-injection. As shown in Table LXV (Appendix E) small, statistically significant or borderline decreases in diastolic and systolic blood pressure as well as pulse rate were observed throughout the post-injection period. These changes were still present at 180 min after injection when the measurements were terminated. Therefore, these observations were not followed to their resolution.

No laboratory measurements were collected in the study.

No deaths were reported in this trial.

8.2 Reviewers' Trial #2 Sponsor's protocol 280 - 32B

- 8.2.1 Sponsor stated objective. Same as in Trial # 1.
- 8.2.2 Design. Same as in Trial # 1.
- 8.2.3 Protocol. Same as in Trial # 1.

8.2.4.1 Population enrolled.

The patient population in this trial included 145 subjects in 23 centers in the US, Canada, England, Belgium, France and Germany. (Appendix A, Table IV). A segment of these patients had a history of PE and DVT (Appendix B). As it turns out, the contrast venography was positive in 82.1% of this patient population (Appendix C). Most of these patients had a recent onset of symptoms or surgery (Appendix D). However, pain/tenderness/ Homan sign was absent only in 12% of cases (Appendix E).

8.2.4.2 Efficacy endpoints outcomes.

The Sponsor enrolled 145 patients in this second pivotal trial and "*imaging was not completed*" on 12. Another patient was imaged too late after the injection and still other was unable to keep lying position (Vol.54, p.67, Table IV,). The Sponsor also excluded as "*ineligible for efficacy*" 9 patients who received (Vol.54, p.69, Table V) less than 70 ug dose and one patient was excluded from efficacy analysis because of smaller dose than 10 mCi.

There were 124 of the 145 available for the efficacy analysis.

There were another 9 patients considered as "*data not evaluable based on efficacy results*" (Vol.54, p.72, Table VI) for various reasons ranging from "indeterminate" call on blind read venography to nonavailability of results on clinical venography, which is unacceptable, because it is irrelevant in comparing the blind read assessments. This brings the total of evaluable patients, after the Sponsor's exclusions, to 115.

As in the first pivotal trial, a comparison of a number of readers, diagnostic groupings and the two procedures is only possible when the same data base is analyzed. It is unacceptable to list the number of evaluable patients as larger than 115 in various sections of the submission such 123 (Vol.54, p. 90, Table XXI), if a sensible comparison is to be made. The use of results calculated per intent-to-treat patients such as 140 (Vol.54, p.93, Table XXIV) provides only a limited information since in many instances only a limited data set per patient is available. The Sponsor tended to bring into the

main analysis and sub-analyses of efficacy data from the patients once pronounced ineligible and unevaluable. This makes an analysis uninterpretable and the issue of efficacy confusing.

The diagnostic agreement between contrast venography and scintigraphic imaging with Acutect was the primary efficacy variable as evident from the Integrated Summary of Effectiveness (Vol.23, 808299, par.5). The primary efficacy data can be found in Volumes 1.55-59.

#### 8.2.4.3 Safety outcomes.

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##### Adverse drug events

The time period for observing and reporting ADEs was not specified in the protocol, otherwise the descriptions of ADEs as well as the Case Report Form are adequate. The latest ADEs reported in this submission had their onset at 100 min and the longest duration of an ADE was 360 min. It is unlikely that observation and reporting went beyond these time periods, but the time period covered by the individual investigators is unknown.

The sponsor reported ADEs for 14 patients out of 145 this trial for a total of 22 ADEs. This makes the proportion 1% for this trial.

The ADEs listed for this trial by the Sponsor include headache, back pain, coma unspecified, fever, hypertonia, hypertension, hypotension, dizziness, convulsion, twitch, paresthesia, agitation, nausea and chest pain.

Of the total of 22 ADEs 2 were considered serious by the Sponsor, 5 were considered moderate and the rest mild. Of all 22 ADEs, 3 ADEs were described as ongoing. Among the severe ADEs one patient had hypertonia and the other had a nonspecified pain.

No subject withdrew from the study and the study was not withheld for any reason. No subject died during the defined duration of the study.

##### Vital signs

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Vital signs were collected at baseline and at 10 min, 30 min, 90 min and 180 min, post-injection. As shown in Table LXIV (Appendix F) a small statistically significant decrease in pulse rate was observed throughout the post-injection period. These changes were still present at 180 min after injection when the measurements were terminated.

Therefore, these observations did not continue until the resolution of abnormalities. In the other pivotal trial there were statistical decreases in diastolic and systolic blood pressure. Those were not seen in this trial.

No laboratory measurements were collected in the study.

No deaths were reported in this trial.

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ON ORIGINAL

### 8.3. Reviewer's Trial #3 Sponsor's protocol 280 - 10

This trial is described by the Sponsor as *"a limited enrollment, nonrandomized, open label study conducted in normal volunteers."* Only 4 women and 6 men took part. Only a small amount of peptide was to be used (20.0 to 26.6 ug, Vol.1.28, p.000030, par.1), however, the line listings (Vol.1.28, p.60) showed the range to be 9 to 11 ug. From the same sources, the dose of radioactivity was to be close to 10 mCi, but it actually

Between this Phase 1 study and the pivotal studies the formulation was changed several times (at least 5x) and the relationship between this original formulation and that used later is uncertain in reference to both safety as well as efficacy. Supposedly efficacy was not a study objective in this trial.

The Sponsor summarized the safety results of the study as follows: *"No adverse events were reported during the study. Minor statistically significant changes in some hematology, clinical chemistry, urinalysis and vital sign parameters were noted. However, the magnitude of these changes was small and no clinically significant changes in these parameters were noted."* Thus, the Sponsor dismissed all the safety results as inconsequential.

The amount of peptide was small ( ) and labeled with : mCi <sup>99m</sup>Tc. Despite the small amount of peptide and small population, the following statistically significant changes were obtained:

for clinical chemistry (Vol.1.28, Table s11): glucose increase at 4 hrs  
albumin increase at 1 hr  
GGT increase at 1 hr, borderline at 4 and 24 hrs  
potassium borderline decrease at 4 hrs  
chloride borderline increase at 4 hrs  
magnesium decrease at 1 and 4 hrs

for hematology (Vol.1.28, Table s10): WBC increase at 1 hr  
RBC increase at 1 hr

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ON ORIGINAL

hemoglobin borderline increase at 4 hrs  
hematocrit increase at 1 hr  
MCV increase at 4 hrs  
MCH increase at 4 hrs  
MCHC borderline increase at 4 hrs  
granulocytes increase at 1 hr

for urinalysis (Vol,1.28, Table s12): specific gravity decrease at 1 hr and 4 hrs  
pH borderline rise in 4 hrs

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ON ORIGINAL

No statistically significant changes were observed in this trial for vital signs which were obtained at baseline and at 5 min, 30 min, 1 hr, 2 hrs, 3 hrs, 4 hrs and 24 hrs post-injection.

Although the Sponsor considered all these results inconsequential at the time, this was not appropriate as it should have been the basis for planning the next safety study. Importance of results of this small trial is limited in view of frequent changes in the drug formulation since. However, it is surprising to find the clinical chemistry, hematology and urinalysis effects even with a 1/10 of the peptide dose which was eventually proposed for clinical use.

No Adverse Events were reported for this study.

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ON ORIGINAL

#### 8.4. Reviewer's Trial #4 Sponsor's protocol 280 - 11

This Phase 1 study was conducted mainly to provide data for biodistribution, pharmacokinetics and dosimetry. It enrolled 18 patients and 2 normals. It utilized one of the to-be-marketed formulations identified after the completion of Phase 3 studies. The labeling efficiency was greater than 90% and each subject received a nominal dose of 100 ug P280 labeled with 20 mCi of <sup>99m</sup>Tc.

A broad spectrum of patients was used in this study ranging in age from 27 years to 81 years, mostly male (14) and white (17), with variable medical history and a number of medications, but all 18 patients were within 10 days of onset of significant signs and symptoms of venous thrombosis, or 10 days following a surgical procedure that was associated with a high risk for developing venous thrombosis.

Vital signs were obtained at baseline, 10 min, 30 min, 90 min, 180 min, 4 hr and 24 hrs. Laboratory chemistries, routine hematologies and urine analyses were done at 3 hrs

and 24 hrs and compared to the baseline.

The sponsor did not statistically analyze the safety data in this trial. The blood pressure and pulse the drug were affected in two patients. In patient 0400004 there was a clinically significant rise in systolic BP at 90 min followed by a clinically significant drop diastolic BP , which continued at 4 and 24 hrs accompanied by a clinically significant rise in pulse at 4 hrs and 24 hrs. The total drop in diastolic BP was for the 24-hour time period ant the pulse increase was . The patient was not followed to resolution of abnormalities.

Patient 0400005 had a clinically significant drop in pulse within 10 min of injection which persisted 24 hrs when the follow-up was stopped. This was related to a concomitant increase in systolic blood pressure which reached a clinically significant level at 90 min and continued at 24 hrs.

Within the time frame of this small trial, clinically significant changes were recorded in several clinical chemistry parameters. Clinically significant increases due to the drug were found in creatinine and BUN in two patients at 24 hrs without a subsequent follow-up and in one other instance BUN/creat ratio became elevated because of the drug injection. Glucose was significantly higher in 7 patients, in some of whom it came down at 24 hrs, but 3 remained elevated at 24 hrs. Surprisingly even triglycerides were elevated in 5 instances out of 20 subjects. Iron was elevated in 7 cases. ALT and AST became simultaneously elevated in one case and there was one additional case each for AST and GGT. Bilirubins were elevated in 9 cases.

The hematology values varied very little throughout the trial.

8.5 Reviewer's trial #5 Sponsor's protocol 280 - 20

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ON ORIGINAL

The intention of this small study in 31 patients was to show the performance of this product in imaging pulmonary thromboembolism and venous thrombosis. A large dose (up to 250ug) of peptide was used either with 10, 20 or 30 mCi <sup>99m</sup>Tc. The study was performed by three different investigators at three medical centers and analyzed either as the total, or individually by centers. One of the trials had at least 16 patients while the other two provided the remaining patients.

The safety evaluation includes only monitoring of ADEs and vital signs. Hematology laboratory data was obtained only in 3 patients and clinical chemistry in none. Mostly pooled data was analyzed, but in some instances the stratification by investigator as well as the radioactive dose was evaluated.

Within this framework the Sponsor reported several instances of statistically significant elevated diastolic blood pressure at 90 min, increase in pulse rate at 5 min and an increase in respiration rate at 90 min.

No other ADEs were reported.

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ON ORIGINAL

In regard to efficacy the Sponsor concluded: *"The patient-based agreement rates between the blinded readers' assessment of VT and the sponsor's assessment were consistent across readers, ranging ... However, the small number of patients studied and the lack of balance across subgroups do not permit definite conclusions regarding efficacy to be drawn."*

8.6 Reviewer's trial #6 Sponsor's protocol 280 - 21

APPEARS THIS WAY  
ON ORIGINAL

The Sponsor's reason for this study was as follows: *"The study was designed as a prospective, open-label enrollment, multicenter clinical trial in patients with a broad range of potential pathophysiological conditions involving activated platelets."* The inclusion criteria are provided in Appendix G attached.

In regard to efficacy eight of thirty patients(8/30) were not compared with the final diagnosis(Appendix H). In the remaining patients, 4 had TIA and the scan supposedly showed positive findings in 3 (however, 7 other TIA patients supposedly did not have the P280 results recorded and in 1 the final diagnosis was not obtained). From 3 PE patients 2 had positive final diagnosis, but none had a positive <sup>99m</sup>Tc-P280 scan. One other patient who was entered as positive for both PE and DVT was found negative by both the scan as well as final diagnosis. Of 2 subjects entered as DVT patients one was found positive and the other negative by both approaches, while a patient entered as with a recurrent DVT was found negative by the scan and positive by the final diagnosis. Another 2 patients with graft were both were found positive by Acutect scan, but only one by the final diagnosis. A patient with atrial thrombosis was found negative by the scan, but positive with final diagnosis, and likewise a patient with MI/PTCA.

Thus, these results could show some promise for TIA and graft patients, but the results for those with DVT and PE do not.

Vital signs were monitored in 4 out of 30 patients and no laboratory studies were obtained. No ADEs were found although monitoring was called for in the protocol.

Regarding efficacy the Sponsor made the following conclusion: *"No efficacy conclusions can be drawn from this study because of the limited number of patients per disease class."*

8.7 Reviewer's trial #7 Sponsor's protocol 280 - 22

APPEARS THIS WAY  
ON ORIGINAL

This trial was designed as a 3 x 3 factorial experiment for the radioactive peptide and dose as independent variables. The same study was done in three centers. An additional patient was studied in a fourth center. The patients enrolled had a Doppler ultrasound positive for venous thrombosis and were within 10 days of onset of significant signs and symptoms of venous thrombosis. These signs and symptoms were not specified in the protocol. The levels of P280 peptide were 20, 50 and 100 ug and the levels of radioactivity 5, 10 and 20 mCi. The Sponsor describes in the narrative that several errors occurred in the assignment of patients to treatment.

The results from the three centers were pooled for analysis. Although some statistically significant effects were noted in reference to safety mainly in hematologic parameters, reliability of these findings is questionable because of the small number of patients enrolled and the analysis used which may not be adequate.

The Sponsor presented discrepant data and interpretation of results in regard to the optimal drug dose. Table XIV in Vol. 32, p.000052 contradicts Figure 1, p. 000055 and Figure 2, p.000056, same volume. Likewise, in narrative on p.000052, par.1, l. 5 it is stated: "*There was no evidence of differences due to peptide or site.*", while the text on p.000055, par.1, l.3 states: "*The 100 ug dose provides better agreement with Doppler ultrasound than either the 20 or 50 ug level.*" The comments above in this section about the inadequacy of this protocol pertain also to the main aspect of the dose ranging study.

8.8 Reviewer's trial #8 Sponsor's protocol 280 - 23

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ON ORIGINAL

This trial was an attempt to visualize potential thrombi in carotid arteries. As reported, the trial concerned a total of 14 subjects out of which 5 were patients and the rest were normal volunteers. The results (Appendix I, Table V) were indeterminate in patients in regard to visualization of thrombi, as the scintigraphy with <sup>99m</sup>Tc-P280 did not show a thrombus when present along with an atherosclerotic plaque, but was positive in two instances where the plaque was present, but thrombus was not. These conclusions were based on institutional findings, not the blind read, but they may be informative regardless. The Sponsor deferred the conclusions until later ostensibly because of absence of the blind read.

Although the population is small there were several abnormal laboratory findings recorded (Appendix J). The most noteworthy of which was a 25% increase in PPT 24 hours after receiving Acutect.

No ADEs were reported in this trial either for patients or normal controls.

8.9 Reviewer's trial #9 Sponsor's protocol 280 - 31

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ON ORIGINAL

This experiment included 22 patients and was conducted to compare the Acutect imaging results with the institutional final diagnosis. No blind read analysis was involved.

The safety aspect considered only ADEs, of which there were none reported, but no vital signs or laboratory measurements were collected.

8.10 Reviewer's trial #10 Sponsor's protocol 280 - 33

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ON ORIGINAL

As the drug formulation had been changed numerous times during the development of this drug product, the FDA requested a repetition of the Phase 1 safety, biodistribution and dosimetry trial with the to-be-marketed formulation. The Sponsor initiated this safety trial after the completion of the Phase 3 efficacy study and labeled it #280-33.

The Sponsor stated on the first page (Vol. 63 p.1) that the trial was a multicenter, open-label study of a single administration of <sup>99m</sup>Tc-P280 to evaluate safety in patients at risk for venous thrombosis. However, as it turns out, only 23 subjects out of 86 (26.7%) had a final diagnosis of venous thrombosis. In regard to efficacy, 11 out of these 23 subjects with venous thrombosis were read as true positive and 12 were read as false negatives.

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ON ORIGINAL

It is relevant to point out that the drug formulation is not particularly stable and that at least 3 different segments of the labeled peptide have been identified by the Sponsor. As the total amount of the drug is supposed to be 100 ug, upon splitting into fragments the amounts of each should be also very small. Consequently, if the drug does not render any other biological activity it should not affect the safety parameters. On the other hand, if the opposite is true and the safety profile is affected, then the Sponsor should be aware of that and make appropriate changes as needed, in the development of the product.

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ON ORIGINAL

Although the sponsor tends to dismiss all the safety findings in this safety study as unrelated to the drug, the temporal and other relationships to the drug injection of changes in vital signs and clinical laboratory parameters are hard to miss. Particularly, since the sponsor set limits in advance as to which change would be considered clinically significant and these changes were observed in a significant number of

patients. It would be very difficult to argue that clinically significant increases in glucose in 20 patients out of 107 at 24 hrs post-injection, as well in 10 for ALT and 11 for AST occurred only by chance. In a smaller number of patients these increases were already apparent 3 hrs post-injection. None of those abnormalities were followed to resolution and, therefore, nothing is known about their extended time course and severity.

Therefore, it is evident that the drug may have an unexplained direct effect on vital signs and separately on liver integrity as evident from the liver enzymes, bilirubin and other minor evidence such as prolongation of PT and PTT, elevated triglycerides or elevated serum iron.

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ON ORIGINAL

In reference to the liver enzymes, the Sponsor did not elaborate whether the same patients had alteration in both transferases and GGT, or the same patient was counted more than once for each abnormal test. As it turns out, this reviewer identified about 16 patients out of 107 who could be classified with clinically significant increases by the limits established appropriately prior to the trial commencement. In those who truly had venous thrombosis clinically(23) 5 had at least one of the liver enzymes elevated 24 hrs following the administration with some of them showing the increase already at 3 hrs. Also out of all the 11 patients who were the true Acutect-positive among all the 107 patients tested, 3 had an elevation in at least one liver enzyme.

Therefore, according to the only available laboratory results in patients with DVT in which the drug was used in a large group of patients, more than 20% had liver enzyme elevations in at least one parameter, but many had two, or more changes. None of the patients was followed sufficiently beyond the 24 hr blood sample, and, thus, nothing is known about potential progression of toxicity, or its resolution.

## 9. Overview of Efficacy.

### 9.1 Population

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ON ORIGINAL

### 9.2 Efficacy Findings and Significance

The Sponsor conducted a number of studies with a variable number of patients in each, but there was not a common approach to evaluation for efficacy. Usually the Sponsor referred to results as only positive or negative without describing the details in primary data which led to these conclusions. This primary data and how to obtain it was not described in the respective protocols.

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ON ORIGINAL

Only in two pivotal studies, with the initial enrollment of 135 and 145 patients and the number of patients eligible for evaluation smaller, in the neighborhood of 101 and 115

patients, respectively, the Sponsor performed a blind read for which a Case Report Form for elements of such data was available. The categories the Sponsor listed on the form are 1) side of extremity, 2) intensity of uptake, 3) shape of lesion and 4) extent of vessel involved. The following sub-categories were available to the blinded readers for their assessment of a positive lesion.

- Side
  - right
  - left
  
- Intensity of uptake
  - slight
  - moderate
  - intense
  
- Shape of lesion
  - circular
  - linear
  - irregular
  
- Extent of vessel involved
  - <1/4
  - 1/4 -<1/2
  - 1/2 -<3/4
  - 3/4+

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ON ORIGINAL

In addition, the blinded readers were instructed by the Blind read criteria for P280 (Appendix K). The results for the regions read positive were provided by the Sponsor as line listings (for example, Vol.52, p.000177 - 000207).

### 9.2.1 Image evaluation

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The assessment of intensity of uptake should be viewed as subjective. The shape of the lesion could be a more objective and specific parameter, but only when limited to the potentially thrombosed vessel and its immediate surroundings. A more quantitative evaluation could be the length of the vessel involved.

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ON ORIGINAL

The Sponsor provided an explanation for what was considered linear versus circular lesion during an instruction session at the Agency after the NDA submission. A rounded area of uptake involving in diameter almost the entire perimeter of a thigh was presented as an example of "circular lesion". Thus, the "circular lesion" could have been pictured as an area many fold (10 or more) larger than the potential deep vein diameter.

In some instances, what is presented as a "linear" lesion could coincide with the diameter of a deep vein, but in majority of instances the resemblance to the shape of a vessel was lost. In addition, an inspection of the line listings reveals that the most frequently used Extent of Vessel category was 3/4+. In many instances the 3/4+ value was used for all the regions of the extremity. This would imply that the imaged thrombus would encompass the entire length of the extremity. Furthermore, there were also numerous instances where a presumed thrombus formation was visualized in the entire length of the extremity within 10 min after the drug injection and was still present at 120 min after the injection of the radiopharmaceutical.

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ON ORIGINAL

This type of data is difficult, if not impossible to conceptualize as a thrombus formation. It could represent an active process along the entire length of the femoral vein, popliteal vein and along the entire knee, in some instances 10 - 20 inches or more in length. That may mean that the endothelium of these veins were involved along the entire course of the vessel.

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ON ORIGINAL

This extent of thrombus formation, along the entire length of the vein may obstruct the vessel, at least in some instances, and therefore, the visualization shortly after the drug injection would not be likely. This was not seen. The Sponsor found, in general, that the time of imaging between 10 min and 120 min does not affect the visualization of the presumed lesions and, thus, it is questionable whether the uptake in the vessel and surrounding areas truly represents the thrombus as the Sponsor claims. It may be recalled that the diagnosis of thrombosis was not based on histopathology or final diagnosis, but only contrast venography, the reliability of which is not proven.

These lesion characteristics and the fact that the blind read instructions rely mainly on the asymmetric uptake are insufficient as the image cannot differentiate between thrombus, thrombophlebitis, nonspecific uptake unrelated to thrombosis or phlebitis and, in some instances, perhaps, even merely blood pool, particularly during early imaging. A variety of related pathologies could present similarly or even identically. For, example, trauma could present as a "circular" uptake as referred to above. Hyperemia could show an increase asymmetrically with the predominance of vascular presence. Nonspecific inflammation or myositis could present as an enhanced uptake in the vessel as well as its vicinity. Atherosclerosis could at a late stage cause disruption of endothelium and activation of platelets focally. Unilateral inflammatory joint disease, injury, posttraumatic states and a number of other conditions could cause asymmetric blood supply in the extremities.

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ON ORIGINAL

In short, the Phase 1 and Phase 2 studies could have focused on potential differentiation between venous thrombosis and phlebitis on the one hand and venous thrombosis and other disease conditions involving activation of platelets on the other.

Had this knowledge been obtained prior to Phase 3 study, a relevant Phase 3 trial could have been designed.

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ON ORIGINAL

Another review concern is the necessity to be able to separate chronic and acute thrombosis. Although the Sponsor claims that the detection rate of chronic venous thrombosis with Acutect is very low based on one of the non-pivotal trials, that trial has to be considered preliminary, as the results were not read blindly and adequate Case Report Forms for evaluation of efficacy were not in place at the time. Therefore, whether the results of pivotal trials would differ any if only chronic venous thrombosis patients instead of those with a suspicion of only acute disease were enrolled, remains to be seen. It may be recalled that the pivotal trials concerned only the patients with the duration of symptoms of 10 days or less.

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ON ORIGINAL

The Sponsor compared efficacy of Acutect in various tables which show the results obtained for different anatomic regions of the lower extremities. The original intention was to compare the specific area of an extremity one-on-one with Acutect and contrast venography. This was not done eventually in the pivotal study and according to the Sponsor's explanation it was necessary to abandon that type of comparison because of large variation among the blinded readers in reading the comparator, contrast venography. Therefore, supposedly, the Sponsor resorted to the majority rule or consensus read in the assessment of the comparator.

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ON ORIGINAL

This reviewer obtained efficacy results from the one-on-one comparison for the right calf region in the first pivotal trial counting separately the results obtained at different times post-injection (Appendix L). When the "sensitivity" of Acutect (for venous thrombosis and thrombophlebitis combined) is calculated on this basis, average value for the three readers and three imaging times is slightly more than 50%. Specificity cannot be estimated reliably because it is not known what the outcome of the imaging is in patients without thrombosis or with phlebitis only, or those with other conditions where activation of platelets occurs. When consensus read for contrast venography, or the majority rule is used, the value for "sensitivity" (for venous thrombosis and thrombophlebitis combined) may be somewhat higher, but it is still on the average , as can be seen from the Statistical Review which was done in parallel (please refer to the Statistical Review).

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ON ORIGINAL

As the ability to diagnose venous thrombosis and thrombophlebitis is low in patients suspected of acute disease, it is of essence to weigh the consequences of making an inaccurate diagnosis. In the patient suspected of venous thrombosis from the symptoms the Sponsor chose in the pivotal study at least four groups of potential outcomes are possible. An imaging study may be positive because of 1) venous thrombosis, 2) phlebitis, or 3) other diseases presenting with activation of platelets, or

be 4) negative. The options #2 and #3 can be overdiagnosed as venous thrombosis because the Sponsor has not demonstrated that they present differently scintigraphically from venous thrombosis. As the option #3 could potentially be excluded by an extensive additional workup, the main concern should be overdiagnosing phlebitis as venous thrombosis.

This misdiagnosis would not be without onward effects, as the diagnosis of venous thrombosis requires treatment with anticoagulants. With low sensitivity of the procedure, or perhaps even with sensitivity as presented by the Sponsor this lack of accurate diagnosis could have potentially grave consequences because the proportion of such patients could be large.

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## 10. Overview of Safety

In large trials, the Sponsor conducted safety evaluations of variable depth. In the first Phase 3 trial of 135 patients only ADEs monitoring was performed without vital signs or labs. In the pivotal safety study (135 and 145 patients), only ADEs monitoring and vital signs were done, but without labs. The last trial of 109 patients was a safety study which included ADEs, vital signs as well as the labs and immunogenicity assessment in 33 patients. These trials differed substantially in the proportion of patients with venous thrombosis based on contrast venography. It was 40%, 80% and 21% in the last three trials, respectively. Therefore, the laboratory data may not reflect the target population, but must suffice in the absence of results from a more desirable patient population.

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### 10.1 Deaths

No deaths attributable to the drug were reported.

### 10.3 Significant/Potentially Significant Events

One serious adverse drug event was reported for Trial #280-11 (Vol.1.29, p.000029, par.4) which was described as follows: *"Subject 4-7, a 77 year-old white male, with a history of degenerative joint disease and surgery for total knee replacement 5 days prior to receiving a single injection of Tc 99-P280 experienced chills and fever approximately 16 minutes post-injection and rigors approximately 2 hours post-injections. This subject had slightly elevated temperature at baseline . . . . These adverse events were considered to be of moderate intensity and due to decreased hemoglobin . . . . and hematocrit . . . . This subject was treated with three units of red blood cells and the events resolved. This subject did not complete the study."*

Two adverse drug events were singled out by the Sponsor for Trial #280-33(Vol.1.63,

p.000039, par. 1) as follows: "Patient 2-11 a 48-year old, white male with normal BUN, creatinine and liver function values experienced mild bradycardia 5 minutes following injection of Tc 99m-P280. This patient's heart rate decreased from 5 minutes post-injection. At 30 min, 60 min and 3 and 24 hours post-injection, the patient's heart rate ranged This period of bradycardia resolved without treatment. This event was unrelated to study drug."

"Patient 7-4 a 45 year old, white female with normal BUN and creatinine values and elevated liver function values (SGPT [normal ]; SGOT [normal 0-42U/L] and LDH [normal 0-250 U/L] experienced tachycardia 6 minutes following Tc 99m-P280 injection. This event was considered to be moderate in intensity. The patients heart rate increased at 5 minutes post-injection, and 30 minutes post-injection. At 60 min, 3 and 24 hours post-injection this patient's heart rate was respectively. This event was unrelated to study drug and most likely due to agitation."

Other remarkable events were described by the Sponsor for Trial #280-30 (Vol.1.38, p. 000078, par 1): " Three of the 135 patients (2.2%; 95% confidence interval 0.6% to 6.5%) had an adverse experience. Two of the events were mild (E1-5 "complained of headache" and W4-25 had "pain in right calf"). The attributability of headache was unknown and the investigator judged the calf pain to be unrelated to the study dug. The third event for Patient E4-11 was severe and was described as "severe left chest pain". It occurred while the patient was being moved and was not belived to be attributed to the study drug. The adverse events for Patients E1-5 and E4-11 were also documented in the CRF as abnormal systemic condition. Patients W4-27 and W4-32 enrolled for the second time, had no adverse events."

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ON ORIGINAL

The only adverse event reported as serious in the pivotal study was a case of hypotension described as "probably related" to drug, moderate intensity, 60 minutes in duration and starting 105 min post-injection (Vol.1.54, p.000142). Treatment was required. Please, see also Appendix M.

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Apparently the same event is described also in the Integrated Summary of Safety (Vol. 1.71, p.000038, par.2), but there the start is noted as 10 min post-injection. The subject was 8 days post-trauma and there wa the drop "... in systolic BP from at 10 min to (extra measurement time) to ; at approximately 60 minutes after injection. The subjects did not exhibit other adverse signs or symptoms and the event was not considered life-threatening. Intravenous fluids were administered to increase pressure. ..."

#### 10.4 Other Events.

### 10.5.1 ADR Incidence Tables fo Pivotal Trials

Adverse drug events when recorded were mostly mild and moderate (Appendix M), the only serious ADE was mentioned in the previous paragraph.

The Sponsor has not presented an easily transferable comprehensive table of Adverse events encompassing the total clinical experience. Instead, a computer printout totalling 53 pages is given (Vol.1.71, p.000143 - 000196). The total number of adverse events is put as 5%, 18/362 in men and 6%, 19/318 in women. This conclusion has several limitations the main among them the large variability among various trials, as can be seen from the summary in Appendix P. This suggests that the monitoring was not done with the same diligence throughout drug development.

It seems that there is some tendency for cardiovascular adverse events in those few serious events noted throughout the trials reported in this submission, but definite conclusion cannot be made as those cases are not too many.

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ON ORIGINAL

### 10.5.2 Laboratory findings, Vital Signs

The pivotal study, which seems to be the most representative of the population in which the drug could be used showed a small effect of the drug on decrease in diastolic and systolic blood pressure and potentially also on pulse. The less representative trial referred to above (#280-33) yielded the clinically significant effect on glucose elevation in about 20% of the subjects, clinically significant elevations in ALT, AST or GGT in about 10% of subjects and related elevations in bilirubin. As it appears in the submission, not a single abnormality was monitored until resolution which makes the interpretation of this data inconclusive.

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ON ORIGINAL

### 10.5.3 Special Studies

The Sponsor performed one special clinical study. In order to assess immunogenicity of the radiopharmaceutical a relative change in the amount of IgG was measured in 33 patients 21 days after the single injection of Acutect. The procedure involved ELISA methodology and, apparently, included attachment to a glass surface of an anti-Acutect antibody obtained in animals to a glass surface. The methodology is described poorly and it is not clear how it could accurately measure the small amount of anti-Acutect antibody, if present.

The Sponsor did not state how sensitive and specific the assay is in the human and whether or not any human antibody was ever measured with this assay.

The Sponsor concluded that no additional amount of IgG was present 21 days after Acutect injection and therefore the drug was not immunogenic. The value of this statement is dubious as a small but potentially harmful quantity of specific anti-Acutect antibodies (in view of the potential repetitive use of the diagnostic) could be potentially present among variable amounts of numerous antibodies with other specificities, if the methodology is inadequate.

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#### 10.5.4 Drug-Demographic Interactions

No drug demographic interactions were observed and recorded.

#### 10.5.6 Drug-Disease Interactions

No drug-disease interactions emerged so far.

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ON ORIGINAL

#### 10.5.7 Risk - Benefit Evaluation

The risk/benefit consideration for this NDA has a separate efficacy component. At the end, it may be reduced to a somewhat stricter interpretation than is commonly the case. Is it worthy to use a poorly defined imaging procedure with a relatively high rate of misdiagnosis or overdiagnosis intended for a relatively high risk population, when even the overdiagnosis will surely result in a treatment which will almost certainly escalate the already existing high risk?

The safety risk judging from the observable ADEs is relatively small, but based on the discrepant frequencies of findings between the two pivotal trials and also the remaining studies it may be underreported. The laboratory data and vital signs show a low risk limited to hepatic and cardiac effects, but the abnormal values were not followed to resolution even when clinically significant, preventing an assessment how serious these events might be. Likewise, immunogenicity of the drug has not been tested adequately, but in spite of that it should be pursued in view of disturbing preclinical safety findings. As mentioned in the introduction, chronic use of the drug in the recommended dose resulted in increase in weight of multiple organs in at least two different species suggestive of edema preceding injury.

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ON ORIGINAL

#### 11. Conclusions

Pharmacologic basis for this drug product has not been unequivocally established. In addition, the preclinical trial in animals likely imaged a non-specific uptake at the site of

surgery. No other animal model of thrombosis was utilized.

The Sponsor has not optimized the dose of the drug, as the report on the determination of the best dose is contradictory. Also, the dose ranging study was inadequate in design and execution. Furthermore, the drug product consists of multiple components and it is not certain what proportion of the dose can actually reach the site of thrombosis. The fate of the radioactive component of the drug is largely unknown. A substantial part of the main nonradioactive component remains in the body beyond 24 hrs.

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ON ORIGINAL

The clinical utility of Acutect has not been established by the clinical studies performed. The Sponsor excluded the patients with chronic venous thrombosis (only patients with signs and symptoms of 10 days or less were enrolled) from the pivotal trials and, therefore, the true difference in the potential ability of the imaging agent to differentiate the two was not established. Likewise, it was not established whether the procedure can differentiate between venous thrombosis and superficial thrombophlebitis. The latter is essential in order to exclude increasing risk in some high risk patients groups for whom this drug is intended by overdiagnosing thrombophlebitis as venous thrombosis and treating with anticoagulants unnecessarily. Notwithstanding this fact, the ability to detect pathology was unacceptably low. Finally, the diagnosis of venous thrombosis was determined in the pivotal study by a comparator comparison only, not independently so that the truth was determined. The characteristics of the lesions as present on the enhanced images, read by blinded readers according to the instructions by the Sponsor and interpreted as positive for venous thrombosis are not conducive to current understanding of thrombus formation, thrombotic process as a whole and thrombus presence in particular.

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Although the occurrence of adverse drug events is relatively low, the pivotal trials showed the drug effect on mild decrease of blood pressure, both systolic and diastolic, and mild decrease in the heart rate. Laboratory studies revealed a clinically significant increase, as pre-set by the Sponsor in advance, in glucose, at least one of the liver enzymes and bilirubins in about 20% patients. There are hints that there could be some effects on renal function as well as PT, PTT and some hematology indicators, but the measurements were not done frequently enough, and, above all, the abnormalities in laboratory parameters were not followed up to resolution. The immunogenicity of the drug has not been evaluated with appropriate methodology. Therefore, the final safety profile assessment should be deferred until the necessary data is available. The preliminary safety profile is acceptable, but this view may be largely influenced by the lack of availability of suitable data.

## 12. Recommendations

This application is not approvable at this time as the clinical utility for the suggested indication has not been demonstrated. Based on the data supplied the clinical use of this drug as intended could result in misdiagnosis, a potential harm of which in its consequences could vastly outweigh its limited unproven benefit. The preliminary safety profile is acceptable, but this view may be largely influenced by the lack of availability of suitable data.

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**Appendix A Distribution of Patients by Country in Pivotal Trials**

**(Text page 13)**

provided by the institutional clinical venography result. This result was established by the review of the contrast venograms by the radiologist at the study site, incorporating clinical history for the patient, but independent of the results of the Technetium Tc 99m P280 institutional read. This approach has been substantiated in the literature<sup>11</sup> as improving diagnostic accuracy of film reads, relative to blinded evaluation. A second alternative benchmark was based on an independent blind reading of the contrast venograms. For this evaluation, performed at the Hamilton Civic Hospital Research Center (Hamilton blind-read), an additional three readers were utilized. For this blind-read, each patient film set was read by each blind reader. In those cases where there was disagreement the discordant interpretations were adjudicated among the three reviewers, thereby eliminating any effect of inter-rater variability on the assessment of Technetium Tc 99m P280 diagnostic performance. These two benchmarks were used for two purposes: one, to be compared to the blind-read clinical venogram results; and two, to be used as alternative truth-standards for assessment of agreement rate, sensitivity and specificity of Technetium Tc 99m P280.

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## 7.2 Study Patients

A total of 280 patients were enrolled under Protocol 280-32, eleven sites enrolled 135 patients in Study 280-32A and 23 sites enrolled 145 patients in Study 280-32B. The sites were located in Belgium, England, France, Germany, Canada and the United States. The distribution of patients by country is provided in Table IV.

COUNTRY	STUDY A	STUDY B	COMBINED
	Number of Patients (Sites)		
Belgium	11 (2)	17 (2)	28 (4)
England	23 (2)	11 (2)	34 (4)
France	0	10 (3)	10 (3)
Germany	0	14 (5)	14 (5)
Canada	52 (2)	57 (5)	109 (7)
US	49 (5)	36 (6)	85 (11)
TOTAL	135 (11)	145 (23)	280 (34)

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A total of 37 (13.2%) of the 280 patients were ineligible for all efficacy evaluations based on protocol inclusion/exclusion specifications or because they did not complete the study as planned. There was an equal proportion of patients judged ineligible in both studies (12.6% and 13.8% for Study A and Study B, respectively). Reasons for ineligibility with the associated number of patients ineligible are provided in Table V.

**Appendix B Patients with History of DVT and PE in Pivotal Trials**

**(Text page 13)**

The frequency distributions of eligible patients with a prior history of deep vein thrombosis (DVT) or pulmonary embolism (PE) are provided in Table IX. A slightly higher percentage of patients (23.9%) in Study B reported a prior history of DVT or PE than in Study A (19.5%).

TABLE

DAY

**TABLE IX. DISTRIBUTION OF DVT AND PE HISTORY, STUDIES 280-32A & B, ELIGIBLE PATIENTS.**

	STUDY A		STUDY B		COMBINED	
	N	%	N	%	N	%
DVT History	19	16.1	32	25.6	51	21.0
PE History	7	5.9	13	10.4	20	8.2
DVT or PE History	23	19.5	35	28.0	58	23.9
Total Eligible Patients	118		125		243	

**7.4 Clinical Signs and Symptoms**

The distribution of days since onset of symptoms or high risk surgery (in the absence of symptoms) to the time of the first study procedure (either venography or Technetium Tc 99m P280 scintigraphy) is provided in Table X for eligible patients. Most patients had signs or symptoms of venous thrombosis. In Study A, one eligible patient had no signs or symptoms and in Study B, eight eligible patients had no signs or symptoms. The nine patients were, however, all post high-risk surgery. In both studies, days since onset ranged from <1 day to 10 days, with patients fairly evenly distributed across the range of days.

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**Appendix C Evaluable Patients with Venous Thrombosis by CV**

**(Text page 13)**

	VT DIAGNOSIS				PTS DONE (ND) <sup>1</sup>
	REGION	NEGATIVE	INDETERM.	POSITIVE	
STUDY A	R. CALF	34 (50.0%)	11 (16.2%)	23 (33.8%)	68 (46)
	R. KNEE	46 (67.6%)	8 (11.8%)	14 (20.6%)	68 (46)
	R. THIGH	49 (72.1%)	10 (14.7%)	9 (13.2%)	68 (46)
	R. ILIAC	29 (67.4%)	12 (27.9%)	2 (4.7%)	43 (71)
	IVC	14 (60.9%)	8 (34.8%)	1 (4.3%)	23 (91)
	L. ILIAC	26 (60.5%)	15 (34.9%)	2 (4.7%)	43 (71)
	L. THIGH	42 (75.0%)	5 (8.9%)	9 (16.1%)	56 (58)
	L. KNEE	41 (73.2%)	3 (5.4%)	12 (21.4%)	56 (58)
	L. CALF	28 (50.0%)	5 (8.9%)	23 (41.1%)	56 (58)
	PATIENT	63 (55.3%)		51 (44.7%)	114
STUDY B	R. CALF	17 (25.4%)	3 (4.5%)	47 (70.1%)	67 (56)
	R. KNEE	38 (56.7%)	6 (9.0%)	23 (34.3%)	67 (56)
	R. THIGH	31 (47.0%)	4 (6.1%)	31 (47.0%)	66 (57)
	R. ILIAC	37 (59.7%)	20 (32.3%)	5 (8.1%)	62 (61)
	IVC	10 (58.8%)	7 (41.2%)	0 (0.0%)	17 (106)
	L. ILIAC	37 (51.4%)	29 (40.3%)	6 (8.3%)	72 (51)
	L. THIGH	40 (51.3%)	3 (3.8%)	35 (44.9%)	78 (45)
	L. KNEE	49 (61.3%)	4 (5.0%)	27 (33.8%)	80 (43)
	L. CALF	24 (30.0%)	8 (10.0%)	48 (60.0%)	80 (43)
	PATIENT	22 (17.9%)		101 (82.1%)	123
COMBINED	R. CALF	51 (37.8%)	14 (10.4%)	70 (51.9%)	135 (102)
	R. KNEE	84 (62.2%)	14 (10.4%)	37 (27.4%)	135 (102)
	R. THIGH	80 (59.7%)	14 (10.4%)	40 (29.9%)	134 (103)
	R. ILIAC	66 (62.9%)	32 (30.5%)	7 (6.7%)	105 (132)
	IVC	24 (60.0%)	15 (37.5%)	1 (2.5%)	40 (197)
	L. ILIAC	63 (54.8%)	44 (38.3%)	8 (7.0%)	115 (122)
	L. THIGH	82 (61.2%)	8 (6.0%)	44 (32.8%)	134 (103)
	L. KNEE	90 (66.2%)	7 (5.1%)	39 (28.7%)	136 (101)
	L. CALF	52 (38.2%)	13 (9.6%)	71 (52.2%)	136 (101)
	PATIENT	85 (35.9%)		152 (64.1%)	237

ND = Patients Not Done.

Clinical Contrast Venography: Diagnosis of VT

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The distribution of patients' diagnosis for venous thrombosis (VT) based on institutional site clinical contrast venography is presented in Table XVIb, by body region and for the patient. Based on clinical venography for the combined studies, 110 (46.2%) of 238 evaluable patients were positive versus 128 (53.8%) negative for VT. There was a higher incidence of positive diagnoses in Study B than Study A (53.7% versus 38.3%), although the difference in percent of positive diagnoses

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**Appendix D Onset of Symptoms in Patients in Pivotal Trials**

**(Text page 13)**

**TABLE X. DISTRIBUTION OF DAYS SINCE ONSET OF SYMPTOMS OR SURGERY, STUDIES 280-32A & B, ELIGIBLE PATIENTS.**

DAYS SINCE ONSET	STUDY A		STUDY B		COMBINED	
	N	%	N	%	N	%
< 1	4	3.4	11	8.8	15	6.2
1	18	15.3	10	8.0	28	11.5
2	13	11.0	13	10.4	26	10.7
3	16	13.6	19	15.2	35	14.4
4	15	12.7	12	9.6	27	11.1
5	13	11.0	13	10.4	26	10.7
6	10	8.5	15	12.0	25	10.3
7	10	8.5	14	11.2	24	9.9
8	10	8.5	9	7.2	19	7.8
9	8	6.8	6	4.8	14	5.8
10	1	0.8	3	2.4	4	1.6
TOTAL	118		125		243	

Investigators were asked to score clinical signs and symptoms in five areas: (1) pain/tenderness/Homans' sign, (2) swelling, (3) increased warmth, (4) erythema, and (5) palpable cord. Each of the nine anatomic regions in the lower extremities/lower abdomen were scored as: negative, indeterminate or positive. Other regions in the lower body could also be specified and scored. Frequency distributions of the clinical observations for each of the five symptoms are provided in Table XI for eligible patients. The score for a patient is taken as positive if one or more regions is positive, indeterminate if at least one region is indeterminate and no region is positive, and negative if all regions are negative.

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**Appendix E Summary of Results for Blood Pressure and Heart Rate.  
Trial A.**

**(Text page 13)**

TABLE LXV. SUMMARY OF RESULTS FOR BLOOD PRESSURE AND PULSE RATE.									
Time	Parameter	Technetium Tc 99m P280				Contrast Venography			
		N	Mean	Std. Dev.	P Sign Rank	N	Mean	Std. Dev.	P Sign Rank
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

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SECTION 13

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**Appendix F Summary of Results for Blood Pressure and Heart Rate.  
Trial B.**

**(Text page 15)**

TABLE LXIV. SUMMARY OF RESULTS FOR BLOOD PRESSURE AND PULSE RATE.

Parameter	Time	Technetium Tc 99m P280				Contrast Venography			
		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

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SECTION 13

**Appendix G Inclusion Criteria in the Trial with Other  
Pathophysiological Conditions .**

**(Text page 20)**

SECTION 11

## 9. INVESTIGATIONAL PLAN

### 9.1 Overall Study Design and Plan

The study was designed as a prospective, open-label, limited enrollment, multicenter clinical trial in patients with a broad range of potential pathophysiological conditions involving activated platelets. Patients were to receive antecubital intravenous injections of 20 mCi/75 kg (0.26 mCi/kg; 100 µg P280 peptide, maximum) of Technetium Tc 99m P280. Images were to be evaluated for increased uptake of radioactivity in the area of suspected pathophysiology. The Technetium Tc 99m P280 study was to be compared with an institutional diagnosis based upon medical history, clinical signs and symptoms and confirmatory diagnostic procedures.

SECTION 12

### 9.2 Discussion of Study Design and Choice of Control Group

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This study was designed to assess the feasibility of Technetium Tc 99m P280 scintigraphic imaging for the detection and localization of pathophysiological conditions characterized by activated platelet involvement. Each patient's independent institutional diagnosis served as the control.

SECTION 13

### 9.3 Selection of Study Population

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#### 9.3.1 Inclusion Criteria

Patients, 18 years or older, with pathophysiological conditions involving activated platelets including acute myocardial infarction or other infarctions; acute thrombotic, embolic, or hemorrhagic CVA; recurrent TIA; recent coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty; unstable myocardial angina or abdominal angina; infectious and inflammatory arthritis; tumors; and suspicion of thrombosis in vascular grafts were eligible to participate in this trial. Patients were to provide written informed consent prior to enrollment in the study.

#### 9.3.2 Exclusion Criteria

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The following patients were to be excluded: pregnant or lactating females, patients unable to remain quietly supine, or with medical conditions (e.g. orthopedic/prosthetic appliances) that prohibit scintigraphy.

SECTION 10

**Appendix H Results in the Study with other Pathophysiological  
Conditions.**

**(Text page 20)**

TABLE VIII. CORRELATION OF P280 RESULTS WITH FINAL DIAGNOSIS.

STUDY SITE	PATIENT NUMBER	DISEASE CLASS	P280 RESULTS	(POS/NEG)	FINAL DIAGNOSIS	(POS/NEG)
2	1	PE	NORMAL STUDY	NEG	BILATERAL PE	POS
	2	TIA	NO FOCAL UPTAKE	NEG	NO SIGNIFICANT HEMORRHAGE OR CLOT SEEN	NEG
	3	RECURR. DVT	NORMAL BILATERAL LOWER EXTREMITIES	NEG	ACUTE DVT LEFT LEG	POS
	4	DVT & PE	NORMAL BIODISTRIBUTION OF TRACER	NEG	NO DOCUMENTED DVT	NEG
	5	TIA	POSITIVE R. CAROTID UPTAKE	POS	NO FINAL DIAGNOSIS	ND
	6	RECURR. DVT	NO EVIDENCE OF ACTIVE DVT	NEG	NO FINAL DIAGNOSIS	ND
	7	PE	NO EVIDENCE OF CLOT	NEG	WIDESPREAD VT; POSITIVE R. PULMONARY ARTERY	POS
	8	PE	NO EVIDENCE OF ACTIVE PLATELET DEPOSITION IN DVT	NEG	NO ACTIVE EMBOLIZATION OR DVT	NEG
	9	PE	FOCAL UPTAKE IN R. POP. VEIN CONSISTENT WITH ACTIVE THROMBUS	POS	NO FINAL DIAGNOSIS	ND
	10	DVT	NO EVIDENCE OF ACTIVATED PLATELETS	NEG	NO DEFINITIVE DIAGNOSIS OF L. SUBCLAV. THROMBUS	NEG
3	1	DVT	VT IN R. CFV, SFV AND PFV	POS	DVT R. FEMORAL VEIN	POS
	2	GRAFT	ACUTE R. LATERAL CALF VENOUS THROMBUS PRESENT	POS	INFECTED GRAFT; NO CONFIRMATORY PROCEDURE FOR VT	ND
	3	PROSTHESIS	NORMAL R. HIP	NEG	NO FINAL DIAGNOSIS	ND
	4	GRAFT	CLOTTED R. FEM-POP GRAFT	POS	CLOTTED R. FEM-POP GRAFT	POS
4	1	ACUTE MI/PTCA	NO ABNORMAL TRACER UPTAKE IN REGION OF CORONARY ARTERIES OR MYOCARDIUM	NEG	ACUTE ANTERIOR MI	POS
5	1	TIA	MODERATE FOCAL INCREASE IN LEFT AT BASE AND JUST BELOW BIFURCATION	POS	BILATERAL CAROTID ARTERY STENOSIS	POS
	2	ATRIAL THROMBOSIS	NO INCREASED ACTIVITY SEEN IN AREA OF L. A. THROMBUS	NEG	LEFT ATRIAL THROMBUS	POS

ND = NOT DONE, NR = NOT RECORDED

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TABLE VIII. CORRELATION OF P280 RESULTS WITH FINAL DIAGNOSIS.

STUDY SITE	PATIENT NUMBER	DISEASE CLASS	P280 RESULTS	(POS/NEG)	FINAL DIAGNOSIS	(POS/NEG)
5	3	TIA	ABNORMAL SCAN WITH INCREASE IN ACTIVITY ON RIGHT GREATER THAN LEFT	POS	CAROTID ARTERY ATHEROSCLEROSIS	POS
	4	TIA	MILD TO MODERATE FOCAL INCREASE AT BASE OF CAROTID ARTERY	POS	BILATERAL CAROTID ATHEROSCLEROSIS	POS
	5	TIA	MILD TO MODERATE INCREASE IN ACTIVITY; NO OVERALL P280 IMPRESSION NOTED	NR	BILATERAL CAROTID ATHEROSCLEROSIS	POS
	6	TIA	MILD TO MODERATE INCREASE IN ACTIVITY; NO OVERALL P280 IMPRESSION NOTED	NR	BILATERAL CAROTID ATHEROSCLEROSIS	POS
	7	TIA	MILD TO MODERATE INCREASE IN ACTIVITY; NO OVERALL P280 IMPRESSION NOTED	NR	BILATERAL CAROTID ATHEROSCLEROSIS	POS
	8	TIA	MILD TO MODERATE INCREASE IN ACTIVITY; NO OVERALL P280 IMPRESSION NOTED	NR	LEFT CAROTID ARTERY ATHEROSCLEROSIS	POS
	9	TIA	MILD TO MODERATE INCREASE IN ACTIVITY; NO OVERALL P280 IMPRESSION NOTED	NR	RIGHT CAROTID STENOSIS	POS
	10	TIA	MILD TO MODERATE INCREASE IN ACTIVITY; NO OVERALL P280 IMPRESSION NOTED	NR	LEFT CAROTID STENOSIS	POS
	11	TIA	MILD TO MODERATE INCREASE IN ACTIVITY; NO OVERALL P280 IMPRESSION NOTED	NR	BILATERAL CAROTID ATHEROSCLEROSIS	POS
	12	ARTERIAL GRAFT	ABNORMAL SCAN WITH INCREASED ACTIVITY IN L. KNEE AREA	POS	LEFT FOOT ISCHEMIA	NR
	13	PTCA	NORMAL FLOW AND PLANAR STUDIES; ABNORMAL SPECT	POS	NO FINAL DIAGNOSIS	ND
	14	PTCA	NO ABNORMAL FOCI OF ACTIVITY	NEG	ATHEROSCLEROTIC HEART DISEASE; UNSTABLE ANGINA	NR
	15	NORMAL CONTROL	15 AND 90 MIN SPECT: SLIGHT INCREASE IN R. CAROTID AREA	NR	NORMAL SUBJECT	NEG

ND = NOT DONE, NR = NOT RECORDED

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**Appendix I Results in Patients With Carotid Artery Pathologies.**

**(Text page 21)**

**TABLE V. SUMMARY OF TECHNETIUM Tc 99m P280 VASCULAR UPTAKE RESULTS AND FINAL INSTITUTIONAL DIAGNOSES FOR PATIENTS**

Patients	Technetium Tc 99m P280 Vascular Uptake		Final Institutional Diagnosis			
	Left Carotid	Right Carotid	Artherosclerotic Plaque Present		Thrombus Present	
			Left Carotid	Right Carotid	Left Carotid	Right Carotid
201	Negative	Negative	Yes	--	Unknown	--
301	Positive	Positive	Yes	--	No	--
302	Indeterminate	Positive	Yes	--	No	--
304	Not Evaluated	Positive	--	Yes	--	No
402	Negative	Negative	Yes	--	Yes	--

\* Based on pathology findings following endarterectomy  
 REF: Appendix 16.2 Listings 16 and 18

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Among the nine healthy volunteers in this study, six had images that showed no vascular uptake of Technetium Tc 99m P280 in either carotid artery, two had indeterminate results and one subject (Subject 306) had markedly increased tracer in both carotid arteries.

11.4.1.2 Agreement Between Blinded Readers and the Final Diagnosis

At the end of the study, after all subjects have completed the study, three experienced nuclear medicine physicians not participating as investigators in this study will conduct a blind evaluation of the images from all subjects. Since this study is on-going these data are not yet available.

11.4.1.3 Organ and Region of Interest Uptake

Regions of interest (ROIs) will be defined by one or more of the blinded readers on each subject's image for the carotid arteries and the heart. Vessel/blood ratios will be derived from these ROIs and used to further assess efficacy. These data will be available only after this study is completed.

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**Appendix J** **Abnormal Clinical Laboratory Values in Patient With**  
**Carotid Artery**  
**Pathologies.**

**(Text page 21)**

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

No deaths or serious adverse events were reported for any patient or healthy volunteer enrolled in this study.

12.4 Clinical Laboratory Evaluations

12.4.1 Clinically Significant Individual Laboratory Changes (Per Protocol)

Per protocol criteria for identifying clinically significant changes in hematology and chemistry values are presented in Section 9.5.1.5 of this report.

12.4.1.1 Clinically Significant Individual Hematology Values

A summary of the incidence of clinically significant changes from baseline in hematology values (defined per protocol) is presented in Appendix 14.2 Table 15. A listing of individual hematology values for patients and healthy volunteers is presented in Appendix 16.2 Listings 19 and 20. A listing of normal ranges for hematology tests is presented in Appendix 16.2 Listing 23.

One patient and one healthy volunteer had a clinically significant change in a hematology parameter according to protocol criteria. Both subjects had normal values at baseline and 24 hour post-injection assessments as follows:

- Patient 201 had a  $\geq 25\%$  increase in partial thromboplastin time from seconds at baseline to seconds at the 24 hour post-injection assessment; and
- Volunteer 308 had a  $\geq 25\%$  increase in monocyte values from at baseline to at the 24 hour post-injection assessment.

Neither post-injection value was considered to be clinically significant by the investigator.

12.4.1.2 Clinically Significant Individual Chemistry Values

A summary of the incidence of clinically significant changes from baseline in chemistry values (defined per protocol) is presented in Appendix 14.2 Table 16. A listing of individual chemistry values for patients and healthy volunteers is presented in Appendix 16.2 Listings 21 and 22. A listing of normal ranges for clinical chemistry tests is presented in Appendix 16.2 Listing 24.

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SECTION 15

APPENDIX 16.1.1

SECTION 13

SECTION 14.1

SECTION 14.2

Clinically significant changes from baseline were observed for one patient and three healthy volunteers for the following chemistry parameters BUN/Urea, creatinine, SGPT and total bilirubin as follows:

- Patient 402 had a BUN/Urea value that was considered to be above the normal range at baseline and increased  $\geq 25\%$  at the 24 hour post-injection assessment
- Volunteer 308 had a creatinine value that was within the normal range at baseline and was high with a  $\geq 25\%$  increase at the 24 hour post-injection assessment
- Volunteer 202 had a SGPT value that was within the normal range at baseline and decreased  $\geq 25\%$  to at the 24 hour post-injection assessment; this value was still within the normal range.
- Volunteer 204 had a total bilirubin value that was normal at baseline and increased  $\geq 25\%$  at a 12 day follow-up visit; this value was still within the normal range.

None of these changes in chemistry parameter values were considered to be clinically significant by the investigator.

#### 12.4.2 Hematology Results

A summary of changes from baseline in hematology is presented for all treated subjects in Appendix 14.2 Table 9.

Twelve (12) of the 14 subjects were assessed for the following hematology parameters at baseline and 24 hours post-injection: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils, platelets, prothrombin time, partial thromboplastin time, red blood cell count and white blood cell count.

For each parameter, the majority of subjects had hematology values that remained within the normal range from baseline to 24 hours post-injection. A few subjects had values that were high or low at baseline and were within the normal range when assessed post-injection.

The following table summarizes subjects with normal hematology values at baseline that shifted to outside the normal range post-injection.

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TABLE VI. SUMMARY OF CHANGES IN HEMATOLOGY PARAMETERS			
HEMATOLOGY PARAMETER	NUMBER (%) SUBJECTS		
	N	NORMAL TO HIGH	NORMAL TO LOW
HEMATOCRIT	13	0	1 (8%)
MONOCYTES	12	1 (8%)	0
PLATELETS	13	0	1 (8%)
PROTHROMBIN TIME	14	1 (7%)	0
PARTIAL THROMBOPLASTIN TIME	14	1 (7%)	1 (7%)
RED BLOOD CELL COUNT	13	0	2 (15%)
WHITE BLOOD CELL COUNT	13	0	1 (8%)

REF.: Appendix 14.2 Table 9

None of these changes were considered to be clinically significant by the investigator.

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12.4.3

Clinical Chemistry Results

A summary of changes from baseline in chemistry values is presented for all treated subjects in Appendix 14.2 Table 10.

Ten (10) of the 14 subjects were assessed for the following chemistry parameters at baseline and 24 hours post-injection: alkaline phosphatase, blood urea nitrogen, creatinine, LDH, SGOT, SGPT, total bilirubin, and total protein.

For each parameter, the majority of subjects had chemistry values that remained within the normal range from baseline to 24 hours post-injection. A few subjects had values that were high or low at baseline and were within the normal range when assessed post-injection.

One subject (8%) had a creatinine value that shifted from normal at baseline to above the normal range 24 hours post-injection. This change was not considered to be clinically significant by the investigator.

12.5

Vital Signs, Physical Findings and Other Observations Related to Safety

A summary of the mean changes in vital sign parameters (including systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature) from baseline to 5, 30, 60 minutes and 3-4 and 18-30 hours post-injection is presented for all

treated subjects in Appendix 14.2 Table 21. A listing of vital sign parameters is presented by subject at baseline and 5, 30, 60 minutes and 3-4 and 18-30 hours post-injection in Appendix 16.2 Listing 14.

No clinically significant changes from baseline to any post-injection time point were observed for any vital sign parameter in any individual patient or healthy volunteer.

12.6

#### Incidence of Signs of Extravasation

A summary of subjects with extravasation is presented in Appendix 14.2 Table 23.

No patient or healthy volunteer showed any post-injection signs of extravasation during this study.

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12.7

#### Safety Conclusions

Technetium Tc 99m P280 was well tolerated by both the patients and healthy volunteers enrolled in this study. No adverse events were reported for any subject during the study.

A small number of subjects had shifts in hematology and chemistry parameters from normal at baseline to outside the normal range post-injection, but no trends were observed for any parameter. No change in any laboratory parameter was considered to be clinically significant by the investigator.

In the opinion of the investigators, no clinically significant changes from baseline to time points post-injection were observed in vital sign parameters for any patient or healthy volunteer. No signs of extravasation were observed in any subject.

13.

### DISCUSSION AND OVERALL CONCLUSIONS

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The objectives of the study are to evaluate the efficacy and safety of Technetium Tc 99m P280 in patients at risk for carotid artery thrombi and to establish the normal uptake of Technetium Tc 99m P280 in the carotid arteries of healthy volunteers.

A total of 14 subjects (five patients and nine healthy volunteers) were assessed for efficacy and safety.

In all cases, radiolabeling efficiency was equal to or in excess of 90%. Subjects received approximately 60-100 µg of radioactively labeled P280. No subject received a Technetium Tc 99m P280 sample labeled with less than 15 mCi technetium-99m.

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**Appendix K Instructions to Blinded Readers of the Pivotal Study  
Results**

**(Text pages 9 and 12)**

## BLIND READ CRITERIA AND TRAINING PROCEDURES FOR P280 READ 2

### READING CRITERIA

#### Single sets:

- 1) Similar segments of deep veins must be compared (superficial vein thrombi should not be called positive)
- 2) A positive study requires asymmetric vascular uptake (with or without superimposed diffuse uptake) in contrast-enhanced images
- 3) Asymmetry must be present in both anterior and posterior projections
- 4) If asymmetry appears only after extreme contrast enhancement, call positive if there is also a diffuse asymmetry, negative if no diffuse asymmetry

#### Full sets:

- 1) Similar segments of deep veins must be compared (superficial vein thrombi should not be called positive)
- 2) A positive study requires asymmetric vascular uptake (with or without superimposed diffuse uptake) in contrast-enhanced images
- 3) Asymmetry must be present in both anterior and posterior projections
- 4) Asymmetry is seen at two or more imaging times
- 5) If asymmetry appears only after extreme contrast enhancement, call positive if there is also a diffuse asymmetry, negative if no diffuse asymmetry

### TRAINING OF BLIND READERS

- 1) Readers will be trained on 20 previously evaluable studies, 5 with definitive true positive images (all 3 c.v. readers agreed and all 3 P280 Read 1 readers agreed), 5 with definitive true negative images (all 3 c.v. readers agreed and all 3 P280 Read 1 readers agreed), 5 with true positive images (2/3 P280 Read 1 readers agreed and 2/3 or all c.v. readers agreed), and 5 with true negative images ((2/3 P280 Read 1 readers agreed and 2/3 or all c.v. readers agreed).
- 2) Each reader will then be tested on 10 previously evaluable studies, 3 with definitive true positive images (all 3 c.v. readers agreed and all 3 P280 Read 1 readers agreed), 3 with definitive true negative images (all 3 c.v. readers agreed and all 3 P280 Read 1 readers agreed), 2 with true positive images (2/3 P280 Read 1 readers agreed and 2/3 or all c.v. readers agreed), and 2 with true negative images (2/3 P280 Read 1 readers agreed and 2/3 or all c.v. readers agreed). These test cases will be reviewed and any missed cases will be discussed to determine why they were missed.
- 3) How individual image sets should be read will then be discussed, i.e., without reference to multiple time points; indeterminate findings will be discouraged unless reader has no reason to choose a positive vs. negative.

## BLIND READ PROCEDURES

- 1) All training will be done with images from the opposite study (i.e., A readers will be trained with B images and vice versa)
- 2) All individual imaging times will be evaluated first, followed by an evaluation of all combined image sets
- 3) Where practicable, images will be expanded/contracted to approximately the same size, with all projections displayed simultaneously or sequentially
- 4) Using gray-scale images, the reader will enhance the contrast to the point where the vessels on one side saturate, at which point asymmetry will be assessed
- 5) Inverse gray-scale and color images should be used to assess problem cases (i.e, cases in which the reader is not sure after step 4); this step must be employed for images that are scanned in

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## CASE REPORT FORM

- 1) The CRF page will be completed, signed and dated by the reader and immediately reviewed by Diatide personnel to ensure no technical errors were recorded (e.g., missed responses, "Not done" checked where the reader verbally indicated "Positive", etc.)
- 2) The supplemental CRF page will be completed for each image set called positive in one or more regions

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**Appendix --L Data for Calculation of Sensitivity by Reader and  
Imaging Time**

**(Text page 26)**

APPENDIX L. Data for Calculation of Sensitivity by Reader and Imaging Time								
READER	TRIAL 280-32A				TRIAL 280-32B			
		10min	60min	120min		10min	60 min	120min
# 4	PP	9	11	9	PP	25	29	21
	PN	19	17	19	PN	24	21	33
	NN	34	31	31	NN	12	15	17
	NP	0	3	3	NP	8	5	3
# 5	PP	19	19	16	PP	20	15	14
	PN	9	9	10	PN	30	33	33
	NN	25	23	25	NN	17	17	16
	NP	8	11	8	NP	2	3	4
# 6	PP	15	15	9	PP	18	18	13
	PN	13	13	19	PN	32	31	35
	NN	31	28	31	NN	19	19	18
	NP	3	6	3	NP	1	1	2

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**Appendix M ADR Incidence Tables for Pivotal Trials**

**(Text pages 28 and 29)**

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TABLE LXIII. ADVERSE EVENTS.						
Patient	Event (COSTART)	Intensity	Min. Post Injection	Duration (Min)	Related To Drug	Treatment
POST Technetium Tc 99m P280						
6-1	Headache	Mild	100	15	Probably Not	None
	Pain	Mild	100	15	Probably Not	None
12-3	Pallor*	Moderate	13	40	Probably Not	Lower limbs up
	Hypotens*	Moderate	13	40	Probably Not	
	Sweat*	Moderate	13	40	Probably Not	
15-7	Headache	Mild	90	90	Probably Not	None
17-1	Pain	Severe	60	59	Probably Not	None
POST CONTRAST VENOGRAPHY						
8-10	Nausea	Moderate	0	30	Probably	None
8-12	Syncope	Mild	0	30	Probably	None
12-4 <sup>1</sup>	Vomit	Mild	10	30	Probably	None
14-2	Nausea	Mild	40	90	Probably	None
15-12	Pain*	Severe	0	360	Probably	Rx required
15-13	Pain	Severe	0	30	Probably	None
15-14	Pain	Moderate	-	-	Probably	None

\* Event considered clinically significant

- Related time not recorded.

<sup>1</sup> Patient not injected with Technetium Tc 99m P280.

All the events following Technetium Tc 99m P280 injection were considered probably not related to the study drug, whereas all the events following contrast venography were considered probably related to the contrast venogram. The most common adverse events, regardless of procedure, were pain (including headache) and nausea. Most adverse events were mild or moderate and did not require treatment. Three severe events occurred, one following injection of Technetium Tc 99m P280, considered "probably not" related to the study drug, and two following contrast venography that were considered "probably related" to the procedure. Four events were considered clinically significant. Patient 12-3 experienced pallor, decreasing blood pressure and sweating, which were treated successfully by having the patient lie down with the lower limbs higher than the pelvis-thorax. Patient 15-2 experienced severe pain at the time of the venography injection that lasted for 6 hours and required treatment.

APPEARS THIS WAY ON ORIGINAL

McNemar's Test was used to compare the two diagnostic procedures with respect to (1) the proportions of patients experiencing one or more adverse event of any attribution and (2) the proportions of patients experiencing one or more adverse event

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TABLE LXIII. ADVERSE EVENTS.						
Patient	Event (COSTART)	Intensity	Min. Post Injection	Duration (Min)	Related To Drug	Treatment
POST Technetium Tc 99m P280						
6-1	Headache	Mild	100	15	Probably Not	None
	Pain	Mild	100	15	Probably Not	None
12-3	Pallor*	Moderate	13	40	Probably Not	Lower limbs up
	Hypotens*	Moderate	13	40	Probably Not	
	Sweat*	Moderate	13	40	Probably Not	
15-7	Headache	Mild	90	90	Probably Not	None
17-1	Pain	Severe	60	59	Probably Not	None
POST CONTRAST VENOGRAPHY						
8-10	Nausea	Moderate	0	30	Probably	None
8-12	Syncope	Mild	0	30	Probably	None
12-4 <sup>1</sup>	Vomit	Mild	10	30	Probably	None
14-2	Nausea	Mild	40	90	Probably	None
15-12	Pain*	Severe	0	360	Probably	Rx required
15-13	Pain	Severe	0	30	Probably	None
15-14	Pain	Moderate	-	-	Probably	None

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\* Event considered clinically significant  
 - Related time not recorded.  
<sup>1</sup> Patient not injected with Technetium Tc 99m P280.

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SECTION 13

All the events following Technetium Tc 99m P280 injection were considered probably not related to the study drug, whereas all the events following contrast venography were considered probably related to the contrast venogram. The most common adverse events, regardless of procedure, were pain (including headache) and nausea. Most adverse events were mild or moderate and did not require treatment. Three severe events occurred, one following injection of Technetium Tc 99m P280, considered "probably not" related to the study drug, and two following contrast venography that were considered "probably related" to the procedure. Four events were considered clinically significant. Patient 12-3 experienced pallor, decreasing blood pressure and sweating, which were treated successfully by having the patient lie down with the lower limbs higher than the pelvis-thorax. Patient 15-2 experienced severe pain at the time of the venography injection that lasted for 6 hours and required treatment.

APPEARS THIS WAY ON ORIGINAL

McNemar's Test was used to compare the two diagnostic procedures with respect to (1) the proportions of patients experiencing one or more adverse event of any attribution and (2) the proportions of patients experiencing one or more adverse event

**Appendix N Efficacy Section of CRF for Non-pivotal Studies.**

**(Text page 9)**

CASE REPORT FORM

Subject 280-32      /      -      /     

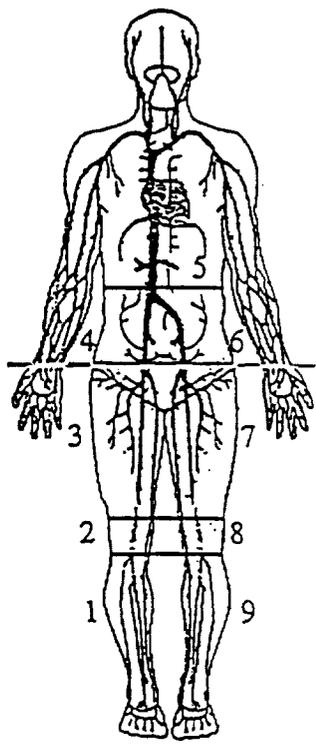
Subject's Initials:      /     

TECHNETIUM Tc 99m P280 STUDY-SITE EVALUATION

Read & score the entire set of images in the aggregate for presence of venous thrombosis. Use anatomical caricature for location identifier. Identify any alternative regions (10-12). Use the comments page to describe any unusual findings, non-vascular uptake, etc.

Impression of all Tc 99m P280 Images:

	<u>Not Done</u>	<u>Negative</u>	<u>Indeterminate</u>	<u>Positive</u>
1. R Calf	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. R Knee	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. R Thigh	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. R Iliac	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. IVC	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. L Iliac	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. L Thigh	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. L Knee	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. L Calf	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



- 1. R Calf
- 2. R Knee
- 3. R Thigh
- 4. R Iliac
- 5. IVC
- 6. L Iliac
- 7. L Thigh
- 8. L Knee
- 9. L Calf

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Signature of Reader

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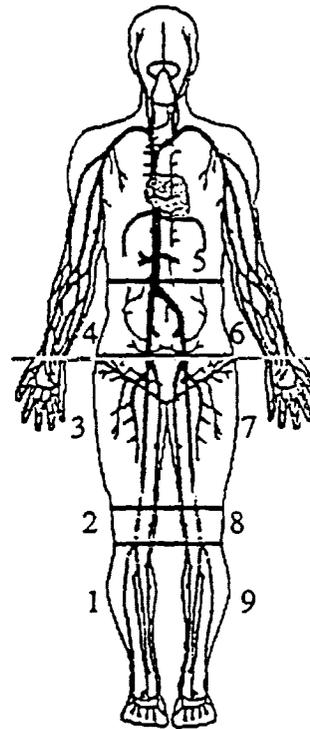
CASE REPORT FORM

Code Number \_\_\_\_\_

BLINDED TECHNETIUM Tc 99m P280 EVALUATION

•Read and score the images for presence of venous thrombosis. Use anatomical caricature as a location identifier. Identify alternative regions if done.

	Not Done	Negative	Indeterminate	Positive
1. R Calf	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. R Knee	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. R Thigh	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. R Iliac	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. IVC	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. L Iliac	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. L Thigh	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. L Knee	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. L Calf	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



- 1. R Calf
- 2. R Knee
- 3. R Thigh
- 4. R Iliac
- 5. IVC
- 6. L Iliac
- 7. L Thigh
- 8. L Knee
- 9. L Calf

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Blinded Reader Signature and Date

000042

**Appendix O Efficacy Section of CRF for the Pivotal Study.**

**(Text page 9)**

Appendix 9

EXAMPLE

Random Code \_\_\_\_\_

Supplemental Case Report Form  
(For regions defined as positive on blinded read)

	Side		Intensity of uptake			Shape of lesion			Extent of vessel involved			
	L	R	Slight	Moderate	Intense	Circular	Linear	Irregular	<1/4	1/4-<1/2	1/2-<3/4	3/4+
<u>10 minutes</u>												
Iliac	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Thigh	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Knee	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Calf	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<u>60 minutes</u>												
Iliac	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Thigh	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Knee	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Calf	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<u>120-180 minutes</u>												
Iliac	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Thigh	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Knee	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Calf	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

7S/  
Reader's Signature

3/9/97  
Date

Random Code \_\_\_\_\_

EXAMPLE

Supplemental Case Report Form  
(For regions defined as positive on blinded read)

	Side		Intensity of uptake			Shape of lesion			Extent of vessel involved			
	L	R	Slight	Moderate	Intense	Circular	Linear	Irregular	<1/4	1/4-<1/2	1/2-<3/4	3/4+
Iliac	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Thigh	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Knee	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Calf	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

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Reader's Signature

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**Appendix P Summary of Dosing and Safety Profile Monitoring**

**(Text page 29)**

APPENDIX P. Summary of Dosing and Safety Profile Monitoring								
Trial #	Adverse Events		Subjects		Dose	Vital Signs	Labs	DVT
	Monitor	##	Patient	Normal				
280-01	+	0	26	-	100ug 20mCi	+	-	N/A
-10	+	0	0	10	9-11ug 20-30mCi	+	+	N/A
-11	+	6/6	18	2	100ug 20mCi	+	only 3	N/A
-20	+	0	31	0	up to 250 10-30mCi	+	-	N/A
-21	+	0	30	0	100ug 20mCi	only 4	-	N/A
-22	+	0	28	0	20-100ug 5-20mCi	+	+	N/A
-23	+	0	5	9	60-100ug 15-20mCi	+	+	N/A
-31	+	0	22	0	30-80ug 12-36mCi	-	-	N/A
-30 (Phase 3)	+	3/3	134	0	20-100ug 10-36mCi	-	-	N/A
-32A (Phase 3)	+	7/4	135	0	100ug 20mCi	+	-	44%
-32B (Phase 3)	+	22/14	145	0	100ug 20mCi	+	-	82%
- 33 (Phase 3)	+	2/2	107	0	46-100ug	+	+	21%

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