

Summary Minutes  
for the  
MEDICAL IMAGING DRUGS ADVISORY COMMITTEE MEETING  
February 9, 1998

6033 '00 FEB -2 P2:27

Food and Drug Administration  
Center for Drug Evaluation and Research  
Holiday Inn-Bethesda, Versailles Ballrooms I and II  
8120 Wisconsin Avenue, Silver Spring, Maryland

Members Present:

Ruth Ramsey, M.D., Chairperson  
Marco Amendola, M.D.  
Laura Boles Ponto, M.D.  
Robert Jahnke, M.D.  
Jonathan Links, M.D.  
Arnold Malcolm, M.D.  
Peter Choyke, M.D.  
Harvey Ziessman, M.D.

Executive Secretary

Leander Madoo

FDA Consultants:

Charles August, M.D.  
Ralph D'Agostino, Ph.D.  
Richard Hammes, R.Ph., M.S.  
Carol Kasper, M.D.  
Marvin Konstam, M.D.  
Charles Rohde, Ph.D.

FDA Participants:

Patricia Love, M.D., M.B.A.  
A. Eric Jones, M.D.  
Adebayo Lanionu, Ph.D.  
Joseph Zolman, M.D., Ph.D.  
Mahboob Sobnan, Ph.D.

Sponsor-Diatide, Inc.:

J. Kris Piper  
H. Dirk Sostman, M.D.  
John Lister-James, Ph.D.  
Richard Dean, Ph.D.  
Jeffrey Ginsberg, M.D.  
Alexander Gottschalk, M.D.  
Raymond Taillefer, M.D.  
Michael Bettman, M.D.

These summary minutes for the February 9, 1998, meeting of the  
**Medical Imaging Drugs Advisory Committee** were approved on  
May 9, 1999.

"I certify that I attended the February 9, 1998, meeting of the  
**Medical Imaging Drugs Advisory Committee** and that these minutes  
accurately reflect what transpired."

Leander B. Madoo

Leander B. Madoo  
Executive Secretary

Ruth H. Ramsey

Ruth H. Ramsey, M.D.  
Chairperson

A Medical Imaging Drugs Advisory Committee (MIDAC) Meeting was held in Open Session from 8:00 a.m. to 3:44 P.M. on February 9, 1998, in Versailles Ballrooms I and II, Holiday Inn, 8120 Wisconsin Ave, Bethesda, Maryland. The purpose of the meeting was to obtain the MIDAC's perspective on the safety and efficacy of new drug application (NDA) 20-887 AcuTect (Technetium Tc99m apcitide having the proposed indication: "For the scintigraphic imaging of acute venous thrombosis". The NDA was submitted by Diatide, Inc. The head table had 12 voting MIDAC panel members. The briefing material conveyed to the MIDAC prior to the meeting included the following: (1) FDA developed draft questions relating to the NDA data, (2) Sponsor prepared briefing document summarizing the NDA data, and (3) FDA briefing Document prepared by the Division of Medical Imaging Drugs, Center for Drug Evaluation and Research.

#### Open Session:

The Chairman, Dr. Ruth G. Ramsey, opened the meeting at 8:00 a.m. Monday, February 9, 1998, and welcomed the committee members and consultants. There were approximately 150 persons in the audience. Mr. Leander Madoo, FDA, delivered a statement of conflict of interest and provided administrative announcements.

#### Conflict of Interest Statement

The Conflict of interest statement noted that full waivers had been granted to Dr. Laura Boles-Ponto and Dr. Marvin Konstam which allowed them full participation and voting on the questions relating to AcuTect, NDA 20-887.

#### Open Public Hearing

There were no requests to speak during the Open Public Hearing, so Dr. Ramsey proceeded to the next topic on the Agenda - committee consideration AcuTect.

**Sponsor Presentation: Diatide, Inc. On NDA 20-887 AcuTect**

Mr. J. Kris Piper, Senior Director Regulatory Affairs - Diatide, provided presentation outline

H. Dirk Sostman, M.D., Diatide Consultant, discussed clinical problems surrounding diagnosis of DVT. He expressed the opinion that AcuTect as an imaging agent will potentially fill some important niches in the clinical work-up of patients, such as the acute versus chronic disease or post operative screening for a symptomatic DVT in high risk populations.

John Lister-James, Ph.D., Senior Director of Research & Development - Diatide, covered AcuTect preclinical issues relating to its mechanism of action. He stated that the data supports AcuTect's specificity of binding to acute venous thrombi.

Richard T. Dean, Ph.D., CEO and Chief Scientific Officer - Diatide, presented an overview of the clinical studies and concluded that the data supports Acutect as being safe and effective for diagnosis of Acute Venous Thrombosis. Dr. Dean's presentation was augmented by the following speakers:

- (1) John Lister-James, Ph.D. - AcuTect Image Reading Criteria;
- (2) Ph.D., Jeffrey Ginsberg, M.D., and Alexander Gottschalk, M.D. - Review of Efficacy Data;
- (3) Raymand Taillefer, M.D. - Review of Case Studies.

Michael Bettman, M.D., Diatide Consultant, discussed venography its application to Deep Vein Thrombosis and diagnostic utility of AcuTect. He concluded the sponsor presentation

**FDA Presentation on NDA 20-887 AcuTect**

Dr. Adebayo Laniyonu, FDA Medical Reviewer (Pharmacologist), Division of Medical Imaging, covered the pharmacology Toxicology issues relating to the NDA.

He agreed that AcuTect labeled peptide binds to activated platelets associated with Acute Deep Venous Thrombosis.

Dr. Joseph Zolman, FDA Medical Officer - Division of Medical Imaging, provided safety evaluation of the NDA. He stated that the FDA review team agrees with the sponsor that the drug is relatively safe, however since only a limited number of patients were monitored beyond three hours there is a lack of information on some potential adverse events.

Dr. A. Eric Jones, Clinical Team Leader Division of Medical Imaging Drug Products, FDA., paraphrased the questions which the committee would be considering in the afternoon. He noted that while venous contrast phlebography was the accepted standard for the NDA studies - it is in reality a comparator rather than a standard.

Dr. Mahboob Sobhan, FDA Statistical Reviewer (Division of Biometrics III) concluded that the AcuTect NDA lacks one of the requirements that there be two adequate and well controlled trials. He stated that pivotal study 280-32A could be considered statistically adequate in support of the indication, but that statistical analysis of pivotal study 280-32B shows rather weak or negative results.

**Questions for Committee AcuTect (apcitide):**

*I. Proof of Concept Relationship to the Proposed Indication*

Implicit in AcuTect's proposed use to Detect Acute venous Thrombosis is the need for apcitide to bind to activated platelets and to preferentially distinguish activated platelets from other cross reacting binding sites in the endothelium. Such distinctions affect AcuTect's potential to affect the differential diagnosis of acute thrombosis, chronic thrombosis, phlebitis, and thrombophlebitis. Also, activated platelets are found in acute thrombosis and in the inflammatory process of phlebitis.

**Question a.** Is there sufficient mechanism of action information to confirm that apcitide binds preferentially to the glycoprotein IIB/IIIA receptor, and that it can distinguish activated platelets from vitronectin receptors in the endothelium?

**Answer:** Several panel members commented that, as worded, the question - "does not matter", rather what matters is if the physician can identify a test that predicts clinical outcome and dictates management.

**Question b.** Is there sufficient Mechanism of action information to support the potential to differentiate acute thrombosis and acute phlebitis?

**Answer:** One member remarked that from the clinical data results one is unable to distinguish positives from negatives. Another member commented that without a gold standard to related positive data to - one has trouble distinguishing between positive and negative results.

## II. *AcuTect Image Technical Features*

The blinded reader instructions identified specific image features found in the AcuTect positive images. The case report forms recorded the information if the images were positive. Similar information on the features of the negative images were not recorded.

**Question:** Is there sufficient information to describe the image features that can distinguish positive and negative results for acute venous thrombosis?

**Answer:** Two committee members stated variability in the interpretation of data stems from study results being marginal at best. Another panel member asserted that anatomic diagnosis depends on the experience of the radiologist doing it and consequently - we may never have absolutes to describe the image features.

### III. Standard of Truth & Efficacy Results

The pivotal phase 3 trials are designed as agreement studies. An external standard of truth (e.g., Histopathology) is not available. Therefore, the assessment of the agreement depends upon the comparator imaging study and, as such, it is important for the results to be blinded.

III. a.) Contrast venography results provided the reference diagnosis. Contrast venography interpretations are influenced by the readers approach or similarity of the criteria used. As such, the results of the contrast venography, and the results of the primary outcome variable are dependent on which blinded read is used to determine the reference diagnosis. The prospectively planned blinded read preserves the independence of the 2 pivotal trials (280-32A and 32B). The Hamilton read is not independent across both studies. Neither blinded read of the contrast venograms used prospectively standardized criteria to interpret the findings.

**Question a.** Which blinded read do you recommend should be used to determine the contrast venography results; ie., the prospectively planned blinded read, or the Hamilton retrospective blinded read? Neither?

**Answer:** The committee consensus was that the Hamilton read results should be used since interpretations were performed by those most experienced and expert. The Hamilton Study had positive results despite its study design limitations.

**Question b.** Is there sufficient information from the agreement of AcuTect and contrast venography results to develop labeling recommendations for clinical?

**Answer:** The committee skipped this question.

Given the above considerations, please respond to the following:

**Question c1.** Do you recommend accepting study 280-32A as one of the 2 pivotal studies to demonstrate the efficacy of AcuTect for Scintigraphic imaging to detect acute venous thrombosis?

**Answer:** The committee voted 11 in favor 1 against for accepting study 280-32A as a pivotal study demonstrating efficacy for AcuTect.

**Question c2.** Do you recommend accepting study 280-32B as one of the 2 pivotal studies to demonstrate the efficacy of AcuTect for scintigraphic imaging to detect acute venous thrombosis (AVT)?

**Answer:** The committee voted 7 in favor and 5 against for accepting study 280-32B as a pivotal study which demonstrates the efficacy of AcuTect to detect AVT. The five panel members who disagreed were concerned with incorporating the Hamilton read data (a post hoc analysis). Also the 5 members against voiced doubts on the overall clinical utility of the pivotal studies; since no insights are achieved knowing that AcuTect is at least 60% in agreement with the reference diagnosis (obtained through contrast venography).

#### IV. Safety

For Patients who received the proposed for market formulation, the database provides the results of adverse event reporting in atleast 6532 patients up to 3 hours and up to 169 patients up to 24 hours. It does not contain data on creatine or liver enzymes at the time points when changes are apt to be detected (if they occur). The in vitro data suggest that apcitide binding can inhibit platelet aggregation. The potential clinical manifestations were not tested with in vivo bleeding time measurements.

**Question:** Is there sufficient information to support the safety and reasonable labeling of AcuTect?.

**Answer:** No major safety issues were raised by the committee, there was agreement that AcuTect is safer than venography.

## VI Approvability of AcuTect

In reference to the considered information, please address the following:

**Question a.** - Do you recommend AcuTect as approvable for "the scintigraphic imaging of acute venous thrombosis"?

**Answer:** 7 panel members voted YES, that AcuTect is approvable; 4 voted No; and one person abstained from voting.

**Question b.** Is there any other indication that you recommend?

**Answer:** The committee do not address this question

**Question c.** If you do not recommend AcuTect as approvable, are there other studies or trial designs that you would recommend be completed before approval?

**Answer:** The 4 panel members who voted against approvability cited the need for further outcome studies and more support of clinical utility of the agent, relative to contrast venography - which provided the reference diagnosis.

**Question d.** If you recommend AcuTect as approvable, are there other studies for efficacy or safety that you would recommend as a phase 4 commitment?

**Answer:** Several members suggested that an open-label prospective (six months in duration) clinical study, using patients with a negative scan, and evaluating for agreed upon important clinical outcome be performed. Also that AcuTect should be compared to current diagnostic technologies: sonography (above the knee) and ultrasound.

Dr. Ramsey thanked the panel, agency, and the sponsor for having participated in the meeting.

The meeting was adjourned at 3:44 p.m.