

UNITED STATES OF AMERICA  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL IMAGING DRUGS ADVISORY COMMITTEE

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MEETING

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Monday, February 9, 1998

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The Advisory Committee met in Versailles Ballrooms I and II, Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Ruth G. Ramsey, M.D., Chairperson, presiding.

PRESENT:

RUTH G. RAMSEY, M.D., Chairman

LEANDER B. MADOO, Executive Secretary

MARCO A. AMENDOLA, M.D., Member

PETER L. CHOYKE, M.D., Member

ROBERT W. JAHNKE, M.D., Member

JONATHAN M. LINKS, Ph.D., Member

LAURA L. BOLES PONTO, Ph.D., Member

CHARLES AUGUST, M.D., Consultant

## PRESENT (Continued):

RALPH D'AGOSTINO, Ph.D., Consultant

RICHARD HAMMES, R.Ph. M.S. B.C.N.P.,  
Consultant

CAROL KASPER, M.D., Consultant

MARVIN KONSTAM, M.D., Consultant

CHARLES ROHDE Ph.D., Consultant

PATRICIA LOVE, M.D., FDA Representative

A. ERIC JONES, M.D., FDA Representative

LILIA TALARICO, M.D., FDA Representative

MICHAEL WELCH, Ph.D., FDA Representative

MICHAEL BETTMAN, M.D., Sponsor  
Representative

RICHARD T. DEAN, Ph.D., Sponsor  
Representative

JEFFREY GINSBERG, M.D., Sponsor  
Representative

ALEXANDER GOTTSCHALK, M.D., Sponsor  
Representative

JOHN LISTER-JAMES, Ph.D., Sponsor  
Representative

J. KRIS PIPER, Sponsor Representative

H. DIRK SOSTMAN, M.D., Sponsor  
Representative

RAYMOND TAILLEFER, M.D., Sponsor  
Representative

ADEBAYO LANIYONU, Ph.D., FDA Reviewer

MAHBOOB SOBHAN, Ph.D., FDA Reviewer

JOSEPH ZOLMAN, M.D., Ph.D., FDA Reviewer

## ALSO PRESENT:

JOHN BALSER, Ph.D.

BOB CARETTA, M.D.

BOB HAGGERTY

KATHLEEN MADSEN, Ph.D.

CHRIS NICODEMUS, M.D.

RICHARD WAHL, M.D.

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(8:02 a.m.)

CHAIRPERSON RAMSEY: Good morning. I'd like to say good morning to everyone in the room, and thank you all very much for coming.

I'm Ruth Ramsey, and I'll be chairing this meeting this morning, and I think probably the best thing for us to do is just to go around the table, and I will have everyone at the table introduce themselves and just briefly your role.

So we can start on the far end. Dr. Jones, next to you if you could nudge -- just introduce yourself.

DR. WELCH: Yes. I'm Mike Welch, Acting Director, Division of Biometrics III, Office of Biostatistics.

DR. JONES: My name is Eric Jones. I'm the clinical team leader in the Division of Medical Imaging Drug Products, FDA.

DR. LOVE: Patricia Love, Division Director of Medical Imaging, FDA.

DR. LINKS: Jonathan Links, Johns Hopkins University, a member of the Committee.

DR. PONTO: Laura Ponto, MIDAC Committee member, University of Iowa.

1 DR. CHOYKE: Pete Choyke. I'm a member of  
2 the Committee. I'm a radiologist at NIH.

3 MR. MADOO: Leander Madoo, FDA.

4 DR. D'AGOSTINO: Ralph D'Agostino, Boston  
5 University, biostatistician.

6 DR. HAMMES: Richard Hammes, a nuclear  
7 pharmacist and professor of pharmacy, University of  
8 Wisconsin, a member of the Committee.

9 DR. KASPER: I'm Carl Kasper, a  
10 hematologist, professor of medicine at the University  
11 of Southern California.

12 DR. JAHNKE: Dr. Robert Jahnke. I'm a  
13 radiologist, member of the Committee from Albuquerque,  
14 New Mexico.

15 DR. AMENDOLA: I'm Marco Amendola,  
16 professor of radiology at the University of Miami and  
17 a member of the Committee.

18 DR. ROHDE: I'm Chuck Rohde. I'm a  
19 biostatistician from Johns Hopkins University.

20 CHAIRPERSON RAMSEY: Thank you very much,  
21 and I'd just like to reintroduce Dr. Patricia Love who  
22 will just say a few words to us this morning.

23 Thank you.

24 DR. LOVE: Thank you very much.

25 I'd just like to also extend regrets from

1 Dr. Paul Botstein, who is unable to be with us this  
2 morning. She is out of town.

3 Also, our Deputy Director, his wife just  
4 delivered twins. So he won't be with us today.

5 You've met Dr. Welch. Some of you who  
6 have been in the meetings earlier, Dr. Nancy Smith was  
7 in this role. There's been some adjustments. So Dr.  
8 Welch is now our Acting Director for Biostatistics, as  
9 was identified, and Dr. Mahboob Sobhan, whom you'll  
10 meet later, is the team leader for statistics.

11 We are looking forward to an exciting day  
12 today. We have a number of very interesting issues to  
13 discuss, but I'll save those other comments until  
14 after the open public session.

15 CHAIRPERSON RAMSEY: Thank you, Dr. Love,  
16 and welcome to everyone here on the Committee.

17 Our next agenda item is the open public  
18 hearing, and at this time --

19 MR. MADOO: Actually, I need to read the  
20 conflict of interest statement and make a couple of  
21 meeting announcements.

22 First of all, welcome, Committee. The  
23 sponsor so kindly has provided us with desk copies of  
24 their presentations. It should be in front of you  
25 with a Boston clip on it.

1           If you examine your blue folders, you'll  
2 note that we have the official meeting agenda. We  
3 also have the actual questions for the meeting.  
4 You'll note that the questions for the meeting are  
5 place in front of you, and they're titled "Issues for  
6 Advisory Committee Discussion," and it's a three-page  
7 scenario, and it has essentially a couple of questions  
8 there terminating with approvability.

9           There's also a couple more items that have  
10 been inserted in your folder. I was presented this  
11 morning with a table that ostensibly relates to the  
12 division briefing document, and it looks like there's  
13 a correction. You might notice there are some data  
14 points arrayed in a table, and it's titled "Number of  
15 Subject Enrolled in the AcuTect Clinical Studies."  
16 I'm sure the division will provide clarification on  
17 that when we reach that point.

18           There's also another item the division has  
19 provided this morning to me, and it looks like it  
20 relates to aspects of their presentation.

21           Let me go ahead, please, and read the  
22 conflict of interest statement for this meeting.

23           The following announcement addresses the  
24 issue of conflict of interest with regard to this  
25 meeting and is made part of the record to preclude

1 even the appearance of such at this meeting.

2 Based on the submitted agenda for the  
3 meeting and all financial interests reported by  
4 Committee participants, it has been determined that  
5 all interests in firms regulated by the Center for  
6 Drug Evaluation and Research present no potential for  
7 an appearance of conflict of interest at this meeting  
8 with the following exceptions.

9 In accordance with 18 USC 2008(b)(3), full  
10 waivers have been granted to Dr. Laura L. Boles Ponto  
11 and Dr. Marvin Konstam. Copies of these waiver  
12 statements may be obtained from the agency's Freedom  
13 of Information Office, Room 12A-30, Parklawn Building.

14 In the event that discussions involve any  
15 other products or firms not already on the agenda for  
16 which an FDA participant has a financial interest, the  
17 participants are aware of the need to exclude  
18 themselves from such involvement, and their exclusion  
19 will be noted for the record.

20 With respect to all other participants, we  
21 ask in the interest of fairness that they address any  
22 current or previous financial involvements with any  
23 firms whose products they may wish to comment upon.

24 And so let me stress we have a floor mic  
25 out there, and as Dr. Ramsey will be chairing the

1 meeting, we do have the opportunity during the open  
2 public hearing for people to come and address the  
3 Committee on germane issues relating to today's  
4 discussion. Please as you come to the mic specify  
5 your name, affiliation, and if you were conveyed by a  
6 sponsor or otherwise.

7 That about entails my comments. I notice  
8 that Dr. Charles August arrived, and we're pleased to  
9 have him, and I might note to Dr. Rohde that Dr. Young  
10 will not be here today. So you might want to move up  
11 one chair and be closer with your colleagues.

12 Thank you very much.

13 CHAIRPERSON RAMSEY: Thank you, Mr. Madoo,  
14 and I certainly didn't mean to exclude you from the  
15 program there, with apologies.

16 We'll next turn to the agenda item  
17 entitled "Open Public Hearing," and at this time  
18 anyone is welcome to step to the microphone.

19 (No response.)

20 CHAIRPERSON RAMSEY: Seeing no one coming  
21 to the open microphone, we'll move on to the next  
22 item, which is the sponsor presentation by Diatide,  
23 Incorporated, and I see on my agenda that the first  
24 speaker would be J. Kris Piper, Senior Director of  
25 Regulatory Affairs of Diatide.

1 MR. PIPER: Good morning. My name is Kris  
2 Piper. I'm Senior Director of Regulatory Affairs at  
3 Diatide.

4 On behalf of Diatide, I'd like to thank  
5 Dr. Love and members of the FDA and Dr. Ramsey and  
6 members of the Committee for giving us this  
7 opportunity today to come and talk to you about the  
8 new drug application for AcuTect.

9 AcuTect is a new radiopharmaceutical  
10 diagnostic imaging agent with a proposed indication  
11 for scintigraphic imaging of acute venous thrombosis.

12 The clinical development of AcuTect began  
13 in 1992, and we submitted the NDA in 1997. This  
14 product has been designated as a priority  
15 classification because currently there exists no  
16 imaging modality that can identify and distinguish  
17 acute venous thrombosis. In addition, as a Technetium  
18 labeled pharmaceutical, AcuTect offers the potential  
19 for safety advantages over iodinated contrast  
20 venograms.

21 With us this morning, we have several  
22 experts in the fields of radiology, nuclear medicine,  
23 and venous thrombosis to help us present our data on  
24 this product. Included is Dr. Bettman, Chief of  
25 Cardiovascular and Interventional Radiology at

1 Dartmouth; Dr. Ginsberg, Director of the  
2 Thromboembolism Unit at Hamilton Research Center; Dr.  
3 Gottschalk, professor of radiology at Michigan State.  
4 Unfortunately Dr. Gottschalk was not able to be with  
5 us personally today, but he wanted to convey his  
6 thoughts to the Committee and was able to provide us  
7 a videotape that we prepared yesterday, and we will be  
8 showing that later on in the program.

9 In addition, we have Dr. Sostman,  
10 professor and Chairman of the Radiology Department at  
11 New York Hospital; and Dr. Raymond Taillefer, Chief of  
12 Nuclear Medicine at the Montreal Hospital and one of  
13 the clinical investigators in our pivotal studies.

14 Presenting for Diatide this morning are  
15 Dr. Lister-James, our Senior Director of Research and  
16 Development, and Dr. Richard Dean, our CEO and Chief  
17 Scientific Officer.

18 The agenda that we will follow this  
19 morning is slightly different than what you have that  
20 was prepared by Mr. Madoo. First, Dr. Sostman will  
21 lead off with a discussion of the clinical situation  
22 involving diagnosis of DVT. Dr. Lister-James will  
23 provide the scientific rationale and discuss the  
24 receptor binding properties and pharmacology of  
25 AcuTect. Following that, Dr. Dean will provide an

1 overview of the clinical study program, and then Dr.  
2 Lister-James will go through a training example of how  
3 we train the blind readers for the AcuTect scans.

4 Dr. Dean will then continue with a  
5 discussion of the efficacy data from the pivotal  
6 trials of AcuTect, and he will be assisted by Dr.  
7 Ginsberg and Dr. Gottschalk.

8 Dr. Raymond Taillefer will then review his  
9 experience with imaging with AcuTect. I might point  
10 out that Dr. Taillefer has done several studies, well  
11 in excess of 40 case studies, using this product and  
12 is quite knowledgeable on it.

13 In conclusion, Dr. Bettman will have some  
14 closing remarks, and Dr. Wyland, who's not shown on  
15 this slide, will also provide some remarks regarding  
16 his experience using AcuTect.

17 As you have seen in the briefing document  
18 that we provided and that FDA provided, today's  
19 discussion is going to focus on the pivotal trials for  
20 this product. These issues that have been raised by  
21 FDA are what we intend to focus our presentation on.

22 In particular, we will discuss the  
23 specific nature of AcuTect's receptor binding; the  
24 fact that AcuTect binds to platelet receptors and does  
25 not bind to endothelial cell receptors; the ability of

1       AcuTect to distinguish acute venous thrombosis from  
2       other causes of leg symptomatology; the fact that  
3       AcuTect performs equally well in patients whether they  
4       are on heparin or other anticoagulants or not; the  
5       rationale for our pivotal trial design and the  
6       proposed efficacy criteria that we selected; the  
7       results of the primary and secondary analyses of  
8       efficacy in our pivotal studies; the decision and the  
9       rationale that we used in selecting the Hamilton  
10       Research Center to conduct a second blind read; and  
11       finally, why we believe that the data presented in the  
12       new application for AcuTect support the proposed  
13       indication of this product as a scintigraphic  
14       imagining agent for venous thrombosis.

15                 With that I'd like to turn the podium over  
16       to Dr. Sostman.

17                 DR. SOSTMAN:    Good morning, ladies and  
18       gentlemen.  As you've already heard, my name is Dirk  
19       Sostman.  I'm professor and Chairman of Radiology at  
20       Cornell Medical College and New York Hospital, and  
21       Diatide has asked me to appear as an independent  
22       expert, having spent many years working in this area,  
23       to indicate something of the context in which this  
24       product application is made.

25                 This disorder, deep vein thrombosis, is a

1 highly prevalent one. Estimates of the annual  
2 incidence range as high as five million cases per  
3 year.

4 It's associated with significant morbid  
5 complications in the form of post phlebitic syndrome,  
6 but perhaps the most devastating complication is that  
7 of pulmonary embolism. Approximately 30 percent of  
8 deep vein thrombi which occur above the knee result in  
9 pulmonary embolism, and approximately 30 percent of  
10 pulmonary emboli are fatal in the absence of therapy.

11 Fortunately, effective therapy is  
12 available in the form of anticoagulants. However, the  
13 problem is that anticoagulants themselves are  
14 associated with significant complications. In the  
15 Pioped study, for example, seven percent of patients  
16 who underwent anticoagulant therapy experienced  
17 significant bleeding complications, such as major  
18 falls in hemoglobin, bleeding into a joint, or  
19 bleeding into the brain.

20 Accordingly, accurate diagnosis is  
21 mandatory, and there are still significant limitations  
22 in diagnostic tests. Clinical diagnosis is well known  
23 to be nonspecific and insensitive, and imaging tests  
24 themselves remain with significant limitations.

25 Just to emphasize the importance of venous

1 imaging in this particular context of clinically  
2 suspected pulmonary embolism, this was really first  
3 underlined by a study from the Hamilton Group in the  
4 early '80s, published in the Annals of Internal  
5 Medicine.

6 Approximately 230 patients with clinically  
7 suspected pulmonary embolism were studied. A hundred  
8 of these had abnormal perfusion lung scans. Of these,  
9 74 underwent pulmonary angiography and bilateral  
10 angiography, and 52 had venous thromboembolic disease,  
11 either pulmonary embolism alone, deep vein thrombosis  
12 alone, or the combination.

13 And in this study, patients with disease  
14 requiring therapy, that is, either DVT or PE, were  
15 detected at rather similar rates by either imaging the  
16 lungs or by imaging the legs with bilateral  
17 venography.

18 The overall prevalence of disease in this  
19 study was approximately 40 percent.

20 However, venography has fallen into some  
21 disuse, and certainly bilateral venography is a very  
22 impractical test primarily because of the occurrence  
23 of complications. Some of these have been reduced  
24 since the publication of these series with the advent  
25 of nonionic contrast material, but there remain

1 significant problems: pain in a significant number of  
2 patients; local inflammatory responses; extravasation  
3 of contrast material with the potential for soft  
4 tissue injury; the actual induction of the disease,  
5 DVT, by the test; and a variety of systemic  
6 complications of iodinated contrast materials, such as  
7 anaphylaxis or renal toxicity.

8 In addition, venography, although it's  
9 considered the in vivo gold standard, is not without  
10 interpretive difficulties. Certainly, a well filled  
11 venograph with no intraluminal filling defects is  
12 widely accepted as negative, and a case like this in  
13 which multiple filling defects are clearly outlined in  
14 the calf and distal popliteal vein is widely accepted  
15 as a positive study, and there is little dispute about  
16 this.

17 However, false negatives do occur, and  
18 this is an example of a DVT which was originally  
19 considered as a negative and really resulting from  
20 vascular overlap. Additional imaging did demonstrate  
21 DVT in this patient.

22 Technical difficulties, such as nonfilling  
23 particularly of the pelvic veins. In this case, the  
24 pelvic veins were poorly filled because of the  
25 presence of extensive bilateral iliac and caval

1 thrombosis, which was demonstrated by bilateral direct  
2 pelvic venography.

3 Even with appropriate technique,  
4 interpretive difficulties can occur. For example,  
5 this patient with narrowing of the iliac vein. Is  
6 this due to inherent neural thrombus or is it do to  
7 extrinsic compression? Additional imaging in this  
8 case, again, demonstrated that this patient had pelvic  
9 DVT.

10 Perhaps the most challenging area for  
11 conventional venography is the detection of acute  
12 thrombus in a patient with prior disease and the  
13 distinction of acute from chronic deep vein  
14 thrombosis.

15 As you can see, multiple collateral  
16 pathways open up in this setting, and residual defects  
17 occur which can be difficult or impossible to  
18 distinguish from acute DVT.

19 Although venography can be difficult to  
20 interpret, it can be inconclusive, and it can be  
21 wrong, and it is not this that has led to its almost  
22 wholesale replacement by ultrasound.

23 However, I would point out that in my  
24 opinion, the selection of a center which does have  
25 extensive current experience with venography as the

1 gold standard read is most appropriate, and I think  
2 the Hamilton Center is arguably the best one in this  
3 hemisphere for that role.

4           However, the replacement of venography by  
5 ultrasound has occurred largely because of the fear of  
6 complications, and just to indicate to you how  
7 wholesale this replacement has been, when I was at  
8 Duke University, we reviewed approximately 300  
9 patients who had venous imaging for the suspicion of  
10 pulmonary embolism. Of these 300 patients, a total of  
11 six underwent contrast venography. The others were  
12 managed with other imaging modalities which were  
13 noninvasive.

14           Chief among these is ultrasound. It's an  
15 excellent test, being both safe and cheap, and in  
16 appropriate settings, it's highly accurate. For  
17 example, in the thigh in the presence of clinically  
18 localizing findings, sensitivity and specificity are  
19 in the 90s in almost all series.

20           However, ultrasound does have significant  
21 diagnostic limitations. Even in the thigh, in the  
22 absence of clinically localizing findings, sensitivity  
23 has been reported as low as 38 percent, and in our  
24 review of the English language literature last year,  
25 approximately 1,800 published cases, the average

1 sensitivity of ultrasound in this setting was  
2 approximately 65 percent.

3 Additionally, ultrasound is more difficult  
4 in the calf and in the pelvis, and the calf  
5 sensitivities have been reported as low as 30 percent,  
6 specificities as low as 85 percent, and the average  
7 sensitivity in the calf in the absence of localizing  
8 findings in our review was 28 percent.

9 Accordingly, although ultrasound is an  
10 excellent test and has been widely adopted, it is not  
11 the answer. Therefore, all the currently used  
12 modalities for venous imaging have limitations,  
13 venography with complications and the iodinated  
14 contrast material; difficulties in distinguishing  
15 acute from chronic thrombosis; and difficulties in  
16 delineating the proximal extent of clot; ultrasound  
17 with reduced accuracy in the calf and pelvis;  
18 significant limitations in distinguishing acute  
19 disease from chronic disease; and reduced sensitivity  
20 in patients without clinically localizing findings.

21 A few centers are using magnetic  
22 resonance, but it is quite expensive, and its  
23 availability is limited, and significant experience is  
24 required because of the presence of flow artifacts  
25 which can look like thrombus.

1           Against this background, for a number of  
2 years investigators have sought a preferential hot  
3 spot clot imaging agent, and this is an example of hot  
4 spot imaging with radiolabeled platelets, an agent  
5 which I personally wasted about two years of my life.

6           This was a good agent if you were willing  
7 to accept that it was not accurate in the presence of  
8 anticoagulants and if you were willing to wait for  
9 several hours for imaging, and both of these  
10 limitations really precluded its widespread clinical  
11 adoption.

12           I've had the opportunity to review the  
13 briefing document for the agent which you're asked to  
14 consider today, P280, and this is an example of a  
15 positive calf DVT with P280.

16           I was not involved in the development of  
17 this agent or in the trials, but I have reviewed the  
18 briefing document, and I would simply comment, if I  
19 may, that it appears to me from this document, first,  
20 that the Hamilton blind read is the appropriate gold  
21 standard, and, second, that the agent appears to be  
22 safe and effective, and my clinical impression is that  
23 it will potentially fill some important niches in the  
24 clinical work-up of patients, such as the acute versus  
25 chronic disease or post operative screening for a

1 symptomatic DVT in high risk populations.

2 That concludes my remarks. I'd like to  
3 thank you for your attention and for the opportunity  
4 to appear before you.

5 The next presentation will be Dr. Lister-  
6 James from Diatide, who will discuss some of the  
7 preclinical and other issues.

8 DR. LISTER-JAMES: Thank you, Dr. Sostman.

9 Good morning, Dr. Ramsey, members of the  
10 Committee, Dr. Love, members of the FDA.

11 In the next few minutes, I'm going to  
12 review the scientific basis of the product AcuTect,  
13 and in particular, I'm going to address the following  
14 points: the need for this product; what is AcuTect;  
15 why it should work; and how it works.

16 Now, the process of thrombosis, it's been  
17 well established that thrombus biochemistry and a  
18 disease state are interrelated, and in particular, the  
19 difference between acute venous thrombosis and chronic  
20 venous thrombosis is characterized more by differences  
21 in biochemistry than by differences in anatomy.

22 You just heard Dr. Sostman address some of  
23 the difficulties inherent in anatomical imaging  
24 techniques. Approaches to imaging acute venous  
25 thrombosis, there have been several approaches,

1 including radiolabeled platelets, which Dr. Sostman  
2 just mentioned, but this procedure has limitations as  
3 he mentioned: inconvenient preparation, blood  
4 clearance that's too long, and problems in sensitivity  
5 in the presence of anticoagulants.

6 I-125 Fibrinogen, which is a scanning  
7 technique, not an imaging technique, which FDA  
8 approved at one time, was shown to be useful for the  
9 detection of acute venous thrombosis. This product  
10 has limitations, not the least of which is it's been  
11 removed from the market because it's a blood product.  
12 It also has slow blood clearance, requiring delayed  
13 scanning.

14 Radiolabeled antibodies have been  
15 investigated for imaging DVT. An example of one of  
16 those papers is shown in this slide.

17 Antibodies are large, complex molecules  
18 with in many cases slow blood clearance. They also  
19 carry with them the potential of an immune response.

20 And, therefore, there was an unmet need  
21 for a rapidly clearing marker of acute venous  
22 thrombosis. AcuTect was designed to fulfill this  
23 unmet need.

24 AcuTect is a product which produces a  
25 radiopharmaceutical, Technetium Tc99m apcitide.

1 Apcitide is a 13 amino acid synthetic peptide. It  
2 contains a binding region for the platelet GPIIb]IIIa  
3 receptor and a Technetium 99m complex.

4 The structure of the radiopharmaceutical  
5 is shown here with a binding region in yellow on the  
6 left and a Technetium complex on the right.

7 The active binding region of AcuTect is an  
8 analog of the arginyl-glycyl-aspartic acid sequence,  
9 also known as the RGD sequence, which is present four  
10 times on the molecule fibrinogen, and the RGD sequence  
11 binds with the GPIIb]IIIa receptor on platelets.

12 In AcuTect the arginine has been replaced  
13 with a synthetic amino acid, and I'll come back to  
14 this point a little bit later because we believe this  
15 modification is important in the receptor specificity  
16 of the agent.

17 So the active binding region is shown here  
18 on the slide on the left. The comparison is the RGD  
19 sequence of the positively charged arginine,  
20 negatively charged aspartic acid, and on the right the  
21 binding region of AcuTect, a synthetic amino acid  
22 positively charged, negatively charged aspartic acid.

23 About the GPIIb]IIIa receptor, this  
24 receptor is expressed only on platelets. It is not  
25 expressed on endothelial cells. It is key in platelet

1 aggregation where it mediates the binding of  
2 fibrinogen platelets in the process of platelet  
3 aggregation. It only binds to fibrinogen when  
4 platelets are activated.

5 This is shown schematically here. These  
6 are platelets that are bound to the extracellular  
7 matrix that are breaking the endothelium. Actually  
8 this adhesion to the extracellular matrix is not  
9 GPIIb]IIIa receptor mediated, but what is mediated by  
10 this receptor is the aggregation of one platelet to  
11 another through the molecule fibrinogen shown by the  
12 three blue dots here.

13 Each platelet contains 50,000 GPIIb]IIIa  
14 receptors expressed on its cell surface, which makes  
15 it one of the most highly expressed cell surface  
16 receptors, and in addition to binding the molecule  
17 fibrinogen, it also binds AcuTect.

18 This is a showing a little bit more detail  
19 here the GPIIb]IIIa receptor on the surface of the  
20 platelet, normally binding fibrinogen, also binds the  
21 active binding region of AcuTect.

22 Why should AcuTect work? It's because  
23 platelets are involved in acute, but not chronic  
24 venous thrombosis, and AcuTect binds to platelets.

25 Going into a little bit more detail

1 regarding deep vein thrombosis, starting with the  
2 original which is normally felt to be regions of  
3 stasis in the lower limbs or breaks in the  
4 endothelium, coupled with the condition of  
5 hypercoaguability, initially it's believed to involve  
6 platelet deposition with subsequent incorporation of  
7 fibrin in red blood cells, and then propagation  
8 proximally with addition of additional platelets and  
9 fibrin.

10 This condition is a condition of acute  
11 venous thrombosis, and thrombus may then go on to  
12 embolize or to organize as is shown schematically in  
13 this slide. Platelet deposition in a venous valve  
14 cusp, formation of the thrombus, propagation  
15 proximally with addition of additional platelets and  
16 fibrin, and then the potential for embolization or to  
17 organization.

18 This condition here is the condition of  
19 acute venous thrombosis, and this is the condition  
20 which is most likely to embolize. Once the thrombosis  
21 becomes organized, it has much less chance of  
22 resulting in embolization.

23 The right-hand side then is the condition  
24 of chronic thrombosis. This is the condition of acute  
25 thrombosis.

1           And so acute venous thrombosis has the  
2 characteristics that it may or may not be occlusive.  
3 It often involves proximal extension of the initial  
4 thrombus. It is unorganized, fragile, and has a high  
5 potential embolization.

6           Platelets are incorporated into the  
7 thrombus in acute thrombosis where they're activated  
8 at the thrombus and where they express the GPIIb/IIIa  
9 receptor.

10           How AcuTect works? Well, it binds to the  
11 GPIIb/IIIa receptor on activated platelets. It does  
12 not bind to endothelial cell receptors. It does not  
13 bind to red or white blood cells, and what is not  
14 bound to the thrombus is cleared rapidly from the  
15 bloodstream.

16           Regarding the affinity of AcuTect for the  
17 receptor, we have determined that the product inhibits  
18 the binding of fibrinogen to the receptor with an IC-  
19 50 of 1.8 nanomolar, indicating a high affinity of the  
20 product for the receptor.

21           And from the literature it has been shown  
22 that fibrinogen has an inhibition constant for  
23 platelets of about 120 nanomolar, indicating that  
24 AcuTect has higher affinity for the receptor than its  
25 normal ligand fibrinogen.

1           Regarding receptor specificity, the  
2 vitronectin receptor is expressed on platelets and  
3 endothelial cells, and the vitronectin receptor is  
4 receptor which is related to the GPIIb]IIIa receptor.  
5 In fact, it has a high degree of homology with the  
6 GPIIb]IIIa receptor, and if one was to expect any  
7 cross-reactivity of AcuTect with another receptor,  
8 this is the one that one would expect it to cross-  
9 react with.

10           We found that AcuTect does not bind to the  
11 vitronectin receptor. With concentrations as high as  
12 1,000 nanomolar, it does not inhibit the binding of  
13 vitronectin to its receptor, and we believe that this  
14 modification or that this selectivity, the receptor  
15 selectivity, is based on the modification of the  
16 binding region of the agent.

17           We also looked at another assay to assess  
18 the binding of AcuTect to the GPIIb]IIIa receptor  
19 using an assay of platelet aggregation since platelet  
20 aggregation is a GPIIb]IIIa receptor mediated -- sorry  
21 -- dependent process, and we looked at the inhibition  
22 of ADP induced platelet aggregation in plasma. This  
23 is with human platelets.

24           The product inhibited the platelet  
25 aggregation with an IC-50 of .38 micromolar,

1       indicating specific binding to the GPIIb/IIIa  
2       receptor, and I should mention here that this is an in  
3       vitro assay to assess or to evaluate the binding of  
4       the agent to the receptor. The maximum theoretical  
5       possible concentration of the product in vivo in a  
6       human does not reach concentrations high enough to  
7       cause any clinically significant platelet aggregation.

8               We also looked at -- we used that  
9       particular assay of inhibition of platelet aggregation  
10      to evaluate the effect of anticoagulants on the  
11      binding of AcuTect to the receptor, and using blood  
12      from patients who had taken aspirin, we found no  
13      change in the ability of AcuTect to inhibit platelet  
14      aggregation, indicating that aspirin does not  
15      interfere with the binding of AcuTect to the receptor.

16              We also looked at the effect of heparin  
17      where we conducted the assay in the presence of the  
18      therapeutically -- a normal therapeutic concentration  
19      of heparin, and again, we found no change in the  
20      inhibition of platelet aggregation by AcuTect when  
21      heparin was present, indicating no effect of heparin  
22      on the binding of AcuTect to the receptor.

23              And as you will see later on in the  
24      clinical data, this is consistent with the clinical  
25      findings that there was no effect on the ability of

1       AcuTect to detect venous thrombosis whether  
2       anticoagulants were used or not.

3               We also looked at the binding of the  
4       radiotracer to human platelets, and we found that the  
5       product bound three times greater to activated  
6       platelets than to resting platelets.

7               We also look at the in vivo thrombus  
8       update in the dog model where an acute venous thrombus  
9       was induced in the femoral vein, and then we were able  
10      to obtain external images of the thrombus, and upon  
11      excision of the thrombus, obtained thrombus-to-blood  
12      ratios of four and thrombus-to-muscle ratios of 11,  
13      indicating the specific binding of AcuTect to acute  
14      venous thrombosis.

15              In terms of general pharmacology and  
16      biodistribution, when Dr. Taillefer later on reviews  
17      the clinical cases, he'll talk a little bit about  
18      biodistribution, but one point I'd like to make here  
19      since the issue of immunogenicity was raised by the  
20      agency is that we conducted a study of this product in  
21      guinea pigs, which reached the peak doses over a two-  
22      week period followed by a challenge dose and saw no  
23      evidence of an immunogenic response.

24              And in addition, in a Phase I study of  
25      about 30 patients, we also saw no immune response, and

1 this is what one would expect inasmuch as the product  
2 a small, synthetic peptide injected intravenously in  
3 low concentration; would not expect an immune response  
4 from this sort of product, as distinct from monoclonal  
5 antibodies.

6 And so in summary, we conclude that based  
7 on the data that I've just presented, that AcuTect  
8 should and does bind specifically to acute venous  
9 thrombi.

10 Now I'd like to turn the floor over to Dr.  
11 Richard Dean, who will present the clinical findings.

12 DR. DEAN: Good morning. I'm Richard  
13 Dean, and I will be leading a discussion and  
14 presenting an overview of the clinical studies to  
15 Diatide in my capacity as Chief Scientific Officer at  
16 Diatide.

17 I'll be assisted in the presentation by  
18 the following individuals who have been previously  
19 introduced to you.

20 The clinical program consisted of a total  
21 of 710 patients. There were five Phase III studies  
22 done. Two of those five Phase III studies constituted  
23 the pivotal studies for efficacy of this product.

24 Safety is indicated on this slide. These  
25 are adverse events occurring in more than one subject

1 in the entire population of 710 patients. As you can  
2 see, in each of these categories, the adverse events  
3 from all causes was one percent or less.

4 Additionally, we had the opportunity  
5 through the pivotal studies of comparing the safety  
6 directly to venography. These data are indicated on  
7 this slide, where we list treatment related adverse  
8 events associated with AcuTect or venography in these  
9 pivotal studies.

10 There's about 270 patients in each of  
11 these populations. As you can see, categories that  
12 were reported are listed here, and the difference  
13 between AcuTect for the total adverse events was  
14 statistically significant.

15 So we can say that compared to venography,  
16 AcuTect is significantly safer.

17 Those constituted the major databases for  
18 the safety of the product. I'd now like to move on to  
19 the efficacy of the product, and to do that I'd first  
20 like to address the pivotal trial design.

21 One of the key things for consideration is  
22 the type of agents we're comparing. There is no  
23 active agent that we can compare this to. So we are  
24 left with comparing it to an anatomical imaging  
25 technique, venography, which is the gold standard.

1           These are the measures. There are two  
2 different types of measures that are performed. So we  
3 have to be mindful of those as we proceed forward in  
4 the study and design the study.

5           Additional information is shown on the  
6 course of the disease here in this cartoon. These are  
7 the three stages. You have a normal going to an  
8 acute. A certain fraction of patients with acute  
9 disease will go on to have a chronic condition as  
10 shown here, and then a certain portion of these will  
11 go on to have an acute event on top of the chronic  
12 event.

13           You can see how AcuTect is expected to  
14 perform, picking up the acute clot, and you can see  
15 the anatomical test, how that is expected to perform,  
16 where this would be either venography or ultrasound,  
17 but in our particular case it was venography in the  
18 pivotal studies.

19           Herein lies part of the problem with this  
20 particular disease, as was outlined with Dr. Sostman,  
21 inasmuch as the anatomical tests have difficulty in  
22 distinguishing these two conditions.

23           This cartoon here also highlights the  
24 potential problem in comparing a biologically active  
25 or physiological test with an anatomical test. The CV

1 is contrast venography.

2 There may be some cases where a  
3 nonocclusive clot may not be picked up by contrast  
4 venography for one reason or another, where AcuTect  
5 may pick that up, and that would bias the study  
6 against AcuTect. Again, we just need to keep these  
7 things in mind.

8 And the major thing that we believe would  
9 bias the study against AcuTect, of course, is old  
10 thrombi for which the anatomical test would indicate  
11 it's a positive, but AcuTect would not be able to  
12 detect acute disease.

13 So with these limitations in mind, we  
14 proceeded with the following staple data, and that is  
15 that AcuTect in venography will have the highest  
16 concordance in acute disease, and it was on that basis  
17 that we designed the entry criteria to capture that  
18 particular condition, and that is each patient was  
19 entered in the trial if he had the onset of symptoms  
20 within ten days or was ten days post surgery.

21 Each patient had both a venogram and an  
22 AcuTect. So it was a within patient study.

23 The efficacy criteria were decided upon  
24 based on three criteria: what was known about  
25 interobserver agreement rates with contrast

1 venography. That had to be taken into account.

2 In addition, the prior experience that we  
3 had with AcuTect was taken into account, as well as  
4 certain limitations that venography may have as you  
5 have seen previously on the slides comparing  
6 anatomical tests to a physiological test.

7 So the target agreement rate we believed  
8 would be possible a priori was 75 percent with a lower  
9 confidence limit of 60 percent. Now, that's not to  
10 indicate that we believed that the agent is that  
11 accurate or not, but this is the prospective design  
12 that was agreed upon before proceeding with the trial.

13 The endpoints in the analyses are  
14 indicated here. As you would expect, the final  
15 clinical diagnosis and the clinical venography reads  
16 had very high agreement. Those agreement rates were  
17 close to 95 percent in each of the studies, Study A  
18 and B.

19 Priority efficacy endpoint is indicated is  
20 indicated down here, which is a comparison of blind  
21 read AcuTect to blind read venography.

22 There were three different readers for  
23 each of the AcuTect images, and there were three  
24 different readers for each of the venogram images.  
25 The venography readers were different than the AcuTect

1 readers.

2 Now, the secondary endpoint was a  
3 comparison of blind read AcuTect to the clinically  
4 interpreted venograms. You expect here that with  
5 additional clinical information, as has been reported  
6 in the literature, that you would have increased  
7 accuracy in assessing the disease.

8 Now, the venograms were evaluated as  
9 follows. There was an institutional venogram  
10 interpretation by a radiologist at the site, and then  
11 there were, again, three certified radiologists blind  
12 to the clinical information.

13 It's important to note right here that  
14 there were no other selection criteria for these  
15 radiologists. It was assumed at this point -- and  
16 these were all U.S. radiologists -- it was assumed at  
17 this point that a certified radiologist selected  
18 randomly across the nation would be an appropriate  
19 gold standard for this particular comparison.

20 Now, one of the questions you may be asked  
21 today is is the institutional venography read an  
22 appropriate gold standard. We offer you the following  
23 information, which would be in consideration of that  
24 question.

25 The percent of venograms that were

1 documented read prior to the AcuTect test are  
2 indicated here. As you can see, they are in the 70  
3 and 80 percent region.

4 The way that was done is by indicating  
5 that on the case report form. So in many cases, the  
6 entry was made and dated, or I would say in all of  
7 these cases the entry was made and dated on the case  
8 report forms prior to the performance of the AcuTect  
9 test.

10 In those cases for which that did not  
11 happen, we followed up and documented by testimony  
12 that the venograms were read without prior knowledge  
13 of the AcuTect result.

14 That's not surprising because in most  
15 institutions venography and nuclear medicine scans are  
16 read in different locations within the institution.

17 AcuTect images were evaluated as follows.  
18 There was an institutional interpretation reported.  
19 Then there were, as in the study indicated, three  
20 independent nuclear medicine physicians blind to the  
21 clinical information.

22 We had initiated the read for the database  
23 using the combined time points. The agency then  
24 requested part way through that exercise that we  
25 conduct the read with both combined time points and

1 each individual time point, blinding each individual  
2 time point to the particular patient to produce a much  
3 more comprehensive data set.

4 We, as a matter of course, decided to  
5 complete this read and report the information and read  
6 two as the requested study performed by the FDA.

7 I'd now like to reintroduce Dr. John  
8 Lister-James, who will review with you the reader  
9 training for the interpretation of the AcuTect images.

10 DR. LISTER-JAMES: If you would bear with  
11 me for a second and let's take a couple of seconds for  
12 the computer to come up.

13 What I'm about to show you briefly is how  
14 we trained our readers for the blind read of AcuTect  
15 scans. The purpose of this part of the presentation  
16 is just to show you the reader training. Dr.  
17 Taillefer later on in the program will review image  
18 characteristics and present case studies.

19 I'd also like to point out that the  
20 quality of the images that you're about to see are not  
21 representative of what the readers saw since they were  
22 trained and read images on a large computer monitor.  
23 Unfortunately the only way to show you all the images  
24 at the same time is to use a projector, which doesn't  
25 do justice to the images.

1           We started out by reviewing the venous  
2 anatomy of the lower limbs, in particular, the  
3 difference between the deep veins and the superficial  
4 veins with the readers, and then went on to review the  
5 blind read criteria with them, which included the  
6 following:

7           That we were looking for linear central,  
8 that's deep venous uptake; asymmetric when comparing  
9 similar segments, one leg to the other; and that the  
10 anterior views and posterior views were to be  
11 consistent with one another.

12           And when they were reading full image  
13 sets, that's three time points, that the thrombus  
14 should be visible at more than one time point.

15           Now, we trained the readers on 20 images.  
16 In the interest of time, I'm going to just show you  
17 three now, and we do have some additional images. If  
18 any member of the panel is interested in seeing  
19 additional studies, I can make those available at a  
20 break.

21           Just to orient you here, there's three  
22 sets of images, three different time points, ten  
23 minutes, 60 minutes, 120 minutes, and in this  
24 particular scanned sets of images, they are presented  
25 as follows: anterior pelvis, thigh, knee, calf, and

1 posterior -- there is no posterior pelvis -- posterior  
2 thigh, knee, and calf, and they're duplicated at each  
3 of the time points.

4 And I should mention here that these are  
5 viewed as viewed by the gamma camera. So this is in  
6 the anterior view the patient's right leg, left leg,  
7 right/left, right/left, right/left, and then on the  
8 posterior view right/left, right/left, right/left.

9 The readers were allowed to use different  
10 gray scales and different color scales. So either  
11 black on white, as shown here, or white on black, and  
12 they were allowed to use a contrast adjustment using  
13 this color bar, which I'm operating now, to adjust the  
14 contrast of the image looking for linear central,  
15 that's deep venous uptake, asymmetric from one leg to  
16 another.

17 Now, this is a negative case, and there's  
18 no asymmetry in any of these images, indicating the  
19 absence of deep vein thrombosis, of acute venous  
20 thrombosis.

21 Turning to a positive image, I think you  
22 may be able to see on this -- well, let me just  
23 reorient you here. In this particular set of  
24 imagines, the anterior studies are on the left, and  
25 the posterior on the right for each of the time

1 points.

2                   And I think without any contrast  
3 enhancement you can see that in the left calf of this  
4 individual at 60 minutes, you can see linear central  
5 uptake in the deep vein of the calf. You can see it  
6 in the anterior view, in the posterior view,  
7 anterior/posterior, and also at 120 minutes,  
8 anterior/posterior.

9                   And this may be -- oops, let me just back  
10 off here. Adjusting the contrast brings it up, makes  
11 it a little bit easier to see. This is just adjusting  
12 the contrast, black on white. It makes the images a  
13 little easier to see.

14                   And also if one should use a color scale  
15 and a little bit of contrast adjustment, then you can  
16 clearly see the thrombus in the calf of this  
17 individual.

18                   Turning to another positive case, this one  
19 is a little bit more difficult to see than the  
20 previous one. It doesn't become immediately apparent  
21 as the images first come up. However, a little bit of  
22 contrast adjustment, you will be able to see that  
23 there is asymmetric uptake in the right thigh of this  
24 patient versus the left thigh. You can see it  
25 anterior and posterior, and you can see here increased

1 uptake in the right popliteal of this individual  
2 versus the left.

3 Now, I should mention here that you can  
4 also see a little bit of superficial venous uptake.  
5 We reviewed this with the readers to indicate to them  
6 that they should not read this as acute deep venous  
7 thrombosis. So we read around that.

8 Also, in some patients there's some uptake  
9 around the knee. This was also not considered to be  
10 deep venous uptake, and in some cases soft tissue  
11 uptake, again, not considered to be deep venous  
12 uptake.

13 What we were looking for is linear  
14 central, that's deep venous uptake, asymmetric one leg  
15 to the other, and again, I think you'll be able to see  
16 in this, again, using color here it makes it a little  
17 bit easier to read, looking at the asymmetry one leg  
18 to the other.

19 So I think I'll stop here, and as I say,  
20 if you'd like to see any more, we can make those  
21 available at the break, and I'd like to turn the floor  
22 back to Dr. Dean.

23 DR. CHOYKE: Can I ask a quick question  
24 about the popliteal areas? They're slightly warmer  
25 because they're more superficial; is that?

1 DR. LISTER-JAMES: If there is deep venous  
2 uptake, they are noticeably different.

3 DR. CHOYKE: No, even in the normal they  
4 were slightly.

5 DR. LISTER-JAMES: Oh, yes, but in a  
6 normal case you'll see no asymmetry that will be  
7 visible in both legs, whereas if there's thrombus  
8 there, then you see asymmetry.

9 DR. DEAN: Thank you, John.

10 I'd now like to review the results of the  
11 trials with you, and the first thing I'm going to show  
12 are demographics.

13 Again, there was about 120 patients in  
14 each of the arms, in the A study and the B study. As  
15 you can see from this table the demographics are  
16 highly consistent, and that'll be important later as  
17 we discuss the outcome of the efficacy trial.

18 And in addition, I'd like to show you what  
19 the presenting signs and symptoms were. Study A is  
20 the blue bar, and Study B is the yellow bars, and down  
21 on the bottom here, the percent of patients that  
22 present with these symptoms.

23 As you can see, again, highly consistent  
24 set of presenting signs and symptoms, again,  
25 consistent with the expectations from out-patient

1 studies in the literature.

2 One additional datum of note is the  
3 clinical background of the study population. These  
4 are patients with prior thrombotic history. These are  
5 important because they can potentially bias the  
6 results against the product, but these are the  
7 approximate prevalences of disease expected, slightly  
8 higher prevalence of prior history in the B study.

9 So how did we do? Here is a summary of  
10 the efficacy results. As you can see with the primary  
11 endpoint, it was met in Study A and it was missed in  
12 Study B.

13 The secondary endpoints, which are a  
14 comparison to institutional venography read, were met  
15 in both the A and the B study.

16 So herein is the problem, and when the  
17 sponsor, the company, saw this data, the first  
18 question we had was: what's going on?

19 And what I want to do now is take you  
20 through our assessment of the data and our findings  
21 and how we basically addressed the data at this point.

22 The first thing we looked at was a  
23 comparison of the agreement rates. This was the  
24 combined data from both studies, and we're comparing  
25 to institutional venography result. Our thought was

1 that institutional venography, since it was the basis  
2 of the treatment decision on the patients, would be a  
3 good calibrating tool to understand what was happening  
4 in these studies.

5 Now, when we did this, we surprisingly  
6 found out that the blind read venography data set's  
7 agreement with the institutional venogram  
8 interpretation was 63 percent, far lower than we would  
9 have expected.

10 We know that there is some compromise in  
11 the ability to get accuracy in a blind read because  
12 you do not have clinical information, but we did not  
13 think it would be that great.

14 Interestingly, the new test was agreeing  
15 with institutional venography to a greater extent.

16 When we pooled patients across both the A  
17 and the B study, this difference was statistically  
18 significant.

19 This is the data set that let us know  
20 exactly where the problem was and exactly what it was.  
21 These are the percent of patients that were  
22 interpreted as positive by the blind read  
23 venographers. Here are the individual readers down  
24 here. This is the majority read, which could consist  
25 of either unanimous or two to one, and by comparison

1 is shown the institutional read over here.

2 Now, this is based on presenting signs and  
3 symptoms and the type of population that was entered  
4 into the study. The literature shows with multiple  
5 references that you would expect about a 40 percent  
6 positive rate of disease within these types of  
7 patients.

8 You can see the institution calibrates  
9 well with that, though it's slightly higher in the B  
10 study, and this might be the effect of prior history,  
11 but noticeable is that A study is reasonably  
12 consistent with that, one reader slightly higher at 56  
13 percent.

14 But if you go to the B study herein is the  
15 problem, is you have two readers that say that 94  
16 percent of the venograms were positive, and one say  
17 that 83 percent of the venograms were positive.

18 When these two are taken into account to  
19 determine the majority read, you get an interpretation  
20 that 82 percent of the cases in that study were  
21 positive, which is clearly wrong, and that was the  
22 problem.

23 So how do you address a problem like that?  
24 Well, one analogy is, you know, you have serum samples  
25 and you're doing a clinical study and they're frozen

1 and you send them out to the core lab and the core lab  
2 came back and it came back with funny numbers that you  
3 didn't expect. What do you do? You go back and you  
4 find a core lab that's well calibrated and you  
5 resubmit the frozen samples.

6 And what we did is we looked around the  
7 literature, checked our network, and determined that  
8 the institution most likely to provide the gold  
9 standard was Hamilton, but before I do that, I just  
10 want to lead you through one little exercise to  
11 exemplify the problem.

12 If you took, going back here, this reader  
13 here, Reader 1 in the B study and Reader 3 in the B  
14 study and asked them to compare themselves against  
15 each other, one is the gold standard comparing itself  
16 to the other as a new test. You would come up with  
17 this result, that there was a 63 percent agreement.  
18 This would not have met the confidence interval in our  
19 study, and it was not statistically significant.

20 So as I alluded to, what we did was we  
21 selected the Hamilton Thrombosis Research Center with  
22 Dr. Jeff Ginsberg and Dr. Jack Hirsh to conduct a  
23 blind read. We were driven here by trying to find out  
24 truth because obviously we didn't have truth in the B  
25 study, as you can see.

1           These are the credentials of the Hamilton  
2           Research Center. It is a center that does a heavy  
3           amount of investigation in venography and venography  
4           related studies. Their venography reading criteria  
5           have been validated in treatment outcome studies, and  
6           that has been reported, and their reading criteria  
7           also has been applied by this group in pivotal studies  
8           for FDA approved products, mostly recently Lovenox and  
9           Normiflo. These are low molecular weight heparin  
10          products that are used for the treatment of DVT. So  
11          you can see why the institution was used for that  
12          purpose.

13                 I'd now like to ask Dr. Jeff Ginsberg at  
14          Hamilton to come up and comment on how the study was  
15          performed, the blind read, how Hamilton conducts  
16          reads, and what some of the problems can be if you  
17          don't have a standardized set of reading criteria, and  
18          what that can mean for the interpretation of  
19          venograms.

20                         DR. GINSBERG: Thank you, Dr. Dean.

21                         I suppose my task here is twofold. One is  
22          to convince you that not only are Canadians pretty  
23          good hockey players, but we also know how to interpret  
24          the venograms.

25                         I'm a senior scientist at the Hamilton

1 Civic Hospital's Research Center and am in charge of  
2 clinical trials of venous thrombosis and have been for  
3 the last six to eight years, and over the last ten to  
4 15 years, we have been adjudicating venograms using a  
5 standardized technique for a variety of different  
6 treatment and prophylaxis studies, and as such, we  
7 continue to have and have had experience adjudicating  
8 anywhere between about three to 800 venograms per  
9 year. So we do have a fair bit of experience with it.

10 As was mentioned before, in the United  
11 States I think what's happening is that the use of  
12 venography is falling off dramatically, and the  
13 routine use of venous ultrasonography has really  
14 replaced contrast venography as the usual test for the  
15 diagnosis of venous thrombosis, and that has really  
16 two effects.

17 One is that because there's only a minimum  
18 number of venograms that's done in each institution,  
19 the institutions that perform these tasks are really  
20 losing some of their skills in the ability to  
21 adequately perform the test.

22 And secondly, it relates to the  
23 interpretation of the test, and again, in an analogous  
24 fashion, the less number of tests that you do, the  
25 worse you are at interpreting the venograms, and in

1 fact, we are seeing that across a number of different  
2 studies, particularly in prophylaxis in venous  
3 thrombosis that are run in the United States, and  
4 we've been asked to be the adjudication committee for  
5 a number of different multi-national trials.

6 Now, how do we adjudicate venograms?  
7 Well, we read them and interpret them and call them  
8 into one of three classifications. In the first  
9 classification, we call the result normal if all of  
10 the proximal veins, in other words, the external  
11 iliac, femoral and popliteal veins are seen and are  
12 normal, and as well if two of the three set of calf  
13 veins, namely, the posterior tibial and peroneal  
14 veins, are seen and are normal. If all of those veins  
15 are visualized and are normal, the contrast venogram  
16 is considered normal.

17 The other end of the spectrum is a  
18 venogram that's diagnostic of venous thrombosis, and  
19 our criteria are very strict for those, and what we  
20 like to see is a constant or persistent intraluminal  
21 filling defect that's seen in two or more views, and  
22 that is the only criteria that we use for the  
23 diagnosis of venous thrombosis.

24 The third criteria is one that we call  
25 indeterminate, and that occurs when any of the areas

1 that I've cited previously is not well visualized or  
2 not adequately visualized, and this has been a little  
3 bit of a bone of controversy, but if you think about  
4 the pathobiology, what might be accounting for lack of  
5 visualization of a venous segment? And there are  
6 really three potential explanations.

7           One is that there could be a technical  
8 problem. In other words, the radiologist injected the  
9 lateral side of the foot and the medial veins are not  
10 being visualized because there's no contrast going up  
11 that side.

12           The second possibility is that there could  
13 be old disease, chronic disease that's not  
14 recanalised, and so that segment of venous thrombosis  
15 or old venous disease is not being visualized.

16           And then there's the third possibility,  
17 and that is that there could be acute venous  
18 thrombosis that's impeding flow.

19           In order to be conservative, we call these  
20 venograms indeterminate because in our experience, the  
21 majority of these cases, in fact, do not represent  
22 acute venous thrombosis. When we get our radiologist  
23 to put a new needle in the center of the foot and  
24 reinject, more often than not, we're able to visualize  
25 the veins completely, and we often seen normal venous

1 flow.

2 So rather than calling that diagnostic of  
3 venous thrombosis, which I think a lot of our American  
4 colleagues do, we interpret those venograms as being  
5 indeterminate.

6 Now, with regards to the process that was  
7 carried on when we interpreted the venograms for  
8 Diatide, there are a couple of important things that  
9 are necessary to realize.

10 First is that we had absolutely no  
11 information about the clinical status of the patients  
12 that we were adjudicating, nor of the P280 or apcitide  
13 results.

14 In addition, we were not informed that  
15 there was any sort of a problem, in other words, that  
16 we were resolving a dispute or that there was any  
17 controversy about the initial interpretation. All we  
18 knew was that we were adjudicating venograms for a  
19 study for clinical use.

20 And the way it was done at a procedural  
21 level is that two of the three experts that we had  
22 would read the venograms simultaneously, and most of  
23 the time once we read the venograms, we would agree,  
24 and we would annotate the results on a mimeographed  
25 piece of paper of our interpretation.

1           About five percent of the time, there was  
2 disagreement among the two reviewers, and in those  
3 situations what we would do is call in a third expert,  
4 and in that situation the majority would rule. We  
5 would have a discussion, and we would annotate the  
6 results and adjudicate the results based on a majority  
7 decision.

8           Now, with any sort of study such as this,  
9 the expectation based on literature review is that the  
10 prevalence of venous thrombosis should be somewhere  
11 between about 15 to 40 percent, and results in excess  
12 of that are really inconsistent with published data.

13           So I'll turn the floor back over to Dr.  
14 Dean.

15           DR. DEAN: Thank you, Dr. Ginsberg.

16           Okay. So that's what was done. That's  
17 how they did it, and now let's look at the outcome of  
18 a comparison of AcuTect to the Hamilton blind read.

19           This is the first data I'd like to show  
20 you, which is a comparison of both of the blind reads  
21 to the institutionally read venograms. What you can  
22 see here immediately is that now the venography test  
23 is agreeing with itself, that is, the blind read  
24 Hamilton venography to the institutionally read  
25 venograms to a much higher degree than the original

1 blind read did with the institutional read.

2 This told us that our hypothesis was  
3 consistent, that the gold standard that was applied  
4 here was flawed, and that Hamilton was more consistent  
5 with expectation.

6 Now, looking at the data further, I want  
7 to show you this triangulation slide. It's like a  
8 double triangulation slide.

9 Here we're comparing now the Hamilton  
10 blind read again to the institutional reads. You can  
11 see the high rate of agreement, as you would expect.  
12 You would expect the institutions to be somewhat more  
13 accurate since they do have the clinical information  
14 on the patient and they have additional tests on the  
15 patient. So it's not inconsistent that you would  
16 expect a slight drop when these were read blindly.

17 Over here is the problem. This is the  
18 problematic situation, which was the original blind  
19 read venograms, and you can see the comparison to  
20 Hamilton right here is very poor. It is somewhat  
21 better over here in the A study, as would have been  
22 reflected from the outcome of the efficacy analysis in  
23 the A study.

24 For those who are interested in  
25 statistics, I'm not a statistician, but my

1 statisticians tell me that the kappa between this  
2 comparison to this comparison is .6, and the kappa  
3 down here is .2.

4 So this looks like we have now a  
5 calibrated gold standard, and the question is: how  
6 does this now compare to the AcuTect test?

7 This slide shows you the data for each  
8 individual reader across both studies. This is the --  
9 these are the AcuTect readers compared to the Hamilton  
10 blind read data.

11 I want to clarify a few things here. We  
12 have an agreement rate. The 60 percent line is going  
13 across here. It's actually slightly higher than it  
14 should be.

15 The aggregate really refers to a majority  
16 of the independent readers. So this could be all  
17 three readers unanimous or it could be two out of the  
18 three readers to come up with this particular term,  
19 aggregate.

20 As you can see, both Study A and Study B  
21 now are consistent as you would expect from the  
22 demographics and the presenting signs and symptoms.  
23 You can also see that AcuTect meets the efficacy  
24 criteria across both studies.

25 A star means that the null hypothesis has

1       been rejected, and the agent performs above the lower  
2       confidence limit of 60 percent, and we have our  
3       statisticians here who can explain that in detail if  
4       need be.

5               So these are the findings in this study,  
6       and I now want to show you the summary of all three  
7       venography reads and a comparison of AcuTect to all  
8       three venography reads. That's indicated on this  
9       slide.

10              Again, when we say "aggregate," we're  
11       talking about a majority of the independent readers,  
12       and read one, of course, was the read that was  
13       initiated prior to the FDA's mandated read two, and as  
14       you can see here, the original blind read failed to  
15       qualify AcuTect according to the efficacy criteria.  
16       However, both the Hamilton blind read and the  
17       institutional blind read did result in AcuTect meeting  
18       the efficacy criteria in both Study B and Study A.

19              Now, before I get into the next slide,  
20       which is the subset analysis, I would like to ask Dr.  
21       Alexander Gottschalk to comment on these findings in  
22       relation to his experience with thromboembolism  
23       primarily in the chest, which is the sequela of this  
24       disease, and the problems that were inherent in the  
25       Pioped study, how those were resolved, how those were

1 addressed, and how they're similar to the situation  
2 here that we're addressing today with AcuTect.

3 Dr. Gottschalk apologizes. He would have  
4 liked to have been here to address you personally, but  
5 as Mr. Piper indicated, he recorded his comments  
6 yesterday, and we have him on video.

7 So Dr. Gottschalk.

8 DR. GOTTSCHALK (via videotape): I was a  
9 member of the Pioped Task Force. I was on the  
10 steering committee, but also I was an active member --  
11 the working group. This, of course, worries about  
12 embolism in the thorax and not in the legs, but I got  
13 interested in this receptor when I heard some of --

14 DR. DEAN: If you'll bear with me for a  
15 second we can just rewind this.

16 DR. GOTTSCHALK: -- Gottschalk. I'm  
17 professor of radiology at -- good morning. I'm Alex  
18 Gottschalk. I'm professor of radiology at Michigan  
19 State University.

20 I apologize to the Committee for not being  
21 able to come before you in person, but as many of you  
22 know, we have a very active visiting professor program  
23 at Michigan State, and I have an eminent radiologist  
24 coming into town this morning, being Monday morning,  
25 and I cannot get back from Washington to take care of

1 him before testifying, and therefore, I apologize, but  
2 will appear before you on videotape.

3 I have had an active interest in venous  
4 thromboembolism for about 30 years, primarily during  
5 my time at Yale when I was a member in the Pioped Task  
6 Force. I was on the steering committee, but also I  
7 was an active member of the Nuclear Medicine Working  
8 Group. This, of course, worries about embolism in the  
9 thorax and not in the legs, but I got interested in  
10 this receptor when I heard some of the data presented  
11 by Raymond Taillefer, who I believe will be before you  
12 this morning, and you will hear him present some of  
13 his data.

14 I was particularly interested because this  
15 tracer shows as a hot spot area acute thromboembolism.  
16 That's a very important concept to me because both in  
17 the legs and both in the thorax the problem of chronic  
18 pulmonary embolism or chronic thromboembolism in the  
19 deep venous system is a difficult one.

20 I'm sure you are familiar with the fact  
21 that ultrasonographers, as well as venographers, have  
22 trouble with the concept of chronic emboli or clot,  
23 and as a result, a tracer that shows the acute clot as  
24 a hot spot is really a wonderful concept.

25 My old chief, Dick Greenspan, used to say

1 and, in fact, presented at one time what he thought  
2 would be a potential tracer for looking at clots in  
3 the lungs. It turned out not to be effective in  
4 anything besides experimental animals, but he said if  
5 we ever found it, it would be the Holy Grail of  
6 imaging for emboli of all sorts, and I think this is  
7 certainly a potential step toward this with this  
8 particular tracer.

9 Now, like most of you, I read the proposal  
10 principally within the last week in preparation for  
11 coming here to try to see what I could do to help the  
12 Diatide company with their presentation. As I read  
13 it, I was impressed by the fact that the gold standard  
14 that they sought out was about four carats of gold and  
15 20 carats of lead.

16 That did not surprise me because I have  
17 been through this type of problem with the  
18 angiographers and pulmonary embolism trials.

19 In the trial of the 1970s, Dick Greenspan,  
20 my old chief, I think one of the finest chest  
21 radiologists in the world and a pioneer in pulmonary  
22 angiography, came across the fact that the  
23 angiographers -- they were three and all good friends  
24 and worked together a lot -- had no trouble making the  
25 diagnosis of pulmonary embolism, but they had a fair

1 amount of trouble, or at least more trouble than they  
2 would have liked, when they actually came to assessing  
3 the clot size in terms of how many segments were  
4 involved, and so forth.

5 As a result of this, when the Pioped trial  
6 came into being, Dick knew he had to convene his  
7 pulmonary angiography group and hold practice  
8 sessions, as well as discussions, of the criteria that  
9 they would use and how they would apply that.

10 In particular, they were very rigorous in  
11 terms of the criteria they would accept. You could  
12 see only the clot. The clot had to be visible either  
13 as a mass within the vessel or impacted in a vessel  
14 such that the trailing end showed up.

15 And what Dick was mostly concerned with  
16 was the fact that in smaller vessels a vascular cut-  
17 off would not be considered emboli unless you could,  
18 in fact, see the trailing edge of the clot, and so he  
19 convened his group, and they practiced discussing this  
20 and reading cases, not Pioped cases, but practice  
21 cases, in an effort to achieve some type of consensus.

22 When I read the data that was presented in  
23 this trial and looked at the discrepancy between the  
24 original venographers of some 35 percent, I said to  
25 myself, "Well, I'll bet I know what happened."

1 Venography, after all, is not quite as good a gold  
2 standard, if you will, as pulmonary angiography. The  
3 criteria are more loose. You can see a clot. You can  
4 see a column of contrast cut off. You can use  
5 collateral vessels, and so on, and I'll say my guess  
6 is that none of this group ever talked to each other,  
7 and probably one of them considered everything  
8 positive to be clot, and another one considered,  
9 "Well, I'm going to be rigorous," and probably accept  
10 only visualization of clots or certainly more  
11 difficult criteria for calling positivity, and as a  
12 result, they varied all over the map.

13 I think it is to Diatide's credit that  
14 they spotted a real problem fairly quickly, and as the  
15 literature points out, a series of DVT patients that  
16 have symptoms should really have only about a 40  
17 percent incidence of positive clots, and here they  
18 were running with 80 percent incidence, and something  
19 didn't ring right, and what didn't ring right was the  
20 fact that they had lead in the gold standard.

21 Now, I think it's fair to say, gee, should  
22 they have been able to spot this ahead of time. Why  
23 didn't they figure that out? Why didn't their  
24 advisory group tell them that this kind of thing could  
25 happen?

1 I think the answer to that is that you  
2 have to have been there once to have an idea of how  
3 much trouble this can cause you, and I think Justice  
4 Greenspan, who is certainly as bright a person as I  
5 know, didn't recognize the fact that he and his two  
6 other colleagues would run into some trouble worrying  
7 about smaller vessels. He didn't correct that until  
8 he got to the second trial, which was the Pioped  
9 trial.

10 It isn't unreasonable to assume that the  
11 company and their advisors, not having been there,  
12 would find this to be or not recognize this as a  
13 potential problem.

14 Now, having recognized it as a problem,  
15 what do you do? Well, I think the answer is you try  
16 to go somewhere where, in fact, people have a rigorous  
17 criteria. People have been there before. People know  
18 the difficulties with the technique of venography and  
19 are prepared to use the same criteria to interpret the  
20 venogram.

21 And they picked out a place that is  
22 renowned for this type of study, and Jack Hirsh is  
23 certainly an international authority on venous  
24 embolism and DVT, and they were very fortunate, I  
25 think, in selecting the group at Hamilton, who are not

1 only renowned in this ability, but also happen to be  
2 the place that the FDA has used for previous trials.

3 In short, they picked out a gold standard  
4 that has something closer to 14 carats than four  
5 carats. It's very difficult to have a 24 carat gold  
6 standard. For example, in Pioped where angiography is  
7 considered to be one of the finest gold standards we  
8 have, you might be interested to know that the same  
9 angiographer reading 72 cases twice, unbeknownst to  
10 him, reading them over again, agreed with himself 89  
11 percent of the time; that the angiographers in Pioped,  
12 using this same concept that was used in this trial,  
13 and that is majority rules, the first two  
14 angiographers reading a case blindly by themselves  
15 agreed with the other angiographer only 80 percent of  
16 the time, and 20 percent of the time they had to call  
17 in a third angiographer to get a majority rule.

18 It was possible to get three different  
19 opinions because they used pulmonary embolism present,  
20 absent or indeterminate, and when that happened, they  
21 brought the case before the whole angiography working  
22 group. That happened about one percent of the time.  
23 So that was not really a problem, and I don't believe  
24 there's any problem like that in this trial.

25 Therefore, it seems to me that it's

1 important to recognize, one, that the data from the  
2 trial, that is, the readings of the peptide, were  
3 never changed. They were the original readings that  
4 were used, and it became clear looking at the data  
5 from just the history -- and it's well known how often  
6 DVT should appear in a population of folks suspected  
7 of having DVT -- that there was something badly amiss  
8 with the interpretation that was being rendered.

9 In my view, it's totally explicable on the  
10 fact that none of their readers, original blind  
11 readers, got together to discuss the criteria that  
12 they would use or even practice.

13 That was my assumption, by the way, as I  
14 read it. I would have bet that that had happened. I  
15 found out later when I talked to people that that, in  
16 fact, had happened, but I see no reason why that  
17 shouldn't have occurred.

18 For example, if you take a pulmonary  
19 angiogram and say, "Well, I will use" -- I'm  
20 Angiographer 1 -- "I will use not only visualization  
21 of clot, but I will use perfusion deficit in the lungs  
22 as a criteria for pulmonary emboli."

23 And Reader 2 says, "I am going to use not  
24 only visualization of clot, but an occasional view of  
25 the perfusion deficit if I think it is clearly the

1        lobar or segmental."

2                    And the third one says, "I will use only  
3        visualization of the clot."

4                    Then the precision of reading the  
5        pulmonary angiogram would fall apart as well, and I  
6        think something like that had to happen with the three  
7        readers in the blind read because nobody ever -- they  
8        did not get together to figure out the criteria that  
9        they used.

10                   This was remedied, I believe, by using the  
11        Hamilton Group where, in fact, they have practiced,  
12        where they have their criteria carefully established,  
13        and where they did just exactly what I have proposed.

14                   I would suggest that when you look at  
15        these data, you simply throw away all the data from  
16        the blind readings because I think the gold standard  
17        is flawed. It is loaded with lead, and I would look  
18        only at the Hamilton data, which has no bearing on the  
19        readings that were made on the peptide, and I would  
20        consider those two together, in which case I think you  
21        have a satisfactory trial.

22                   DR. DEAN: Thank you, Dr. Gottschalk.

23                   Okay. I'm now going to, as we previewed  
24        before, show you a subset analysis, and there's a lot  
25        of information on this slide, and let me walk you

1 through this.

2 The subset analyses were performed on the  
3 combined studies. These are all AcuTect reads down  
4 here versus the Hamilton blind read, which is now our  
5 14 carat gold standard. These are blind read AcuTect  
6 studies, and these are the site's interpretations of  
7 AcuTect.

8 We have agreement rates, sensitivity, and  
9 specificity. Blue is all the evaluable patients in  
10 the study. Pink is the subset where we've removed  
11 patients with a prior history, which may confound the  
12 results or bias the study against AcuTect, as we have  
13 seen, and red indicates those patients in the narrow  
14 window of within three days of onset of signs and  
15 symptoms, which would be the most narrow window we  
16 could get a reasonable amount of patients to compare  
17 very close to the onset of disease.

18 I'd now like to ask Dr. Ginsberg to come  
19 back up to the podium and comment on this.

20 DR. GINSBERG: Thank you, again, Dr. Dean.

21 I suppose I'd like to wax a little  
22 philosophical, but as an individual who belongs to a  
23 group that sees about 1,200 patients with suspected  
24 DVT per year, the biggest nightmare that I have in  
25 medicine, anyway, relates to the patient with previous

1 disease.

2 And as was exemplified by slides shown  
3 previously, about a quarter of patients who present  
4 have a history of previous disease, and in these  
5 patients, the nightmare that we have is that we really  
6 don't have a gold standard, nor do we even have a very  
7 good test for the diagnosis or exclusion of venous  
8 thrombosis.

9 And let me give you some examples. Of 100  
10 patients who present with suspected recurrent DVT or  
11 who have previous DVT, about 50 percent will develop  
12 post thrombotic syndrome or post phlebitic syndrome.  
13 Those syndromes can be indistinguishable clinically  
14 from recurrent venous thrombosis. So when those  
15 patients present, the clinician is left with a  
16 conundrum of knowing whether or not this is post  
17 phlebitic syndrome or new thrombosis.

18 That is compounded with the recent  
19 observation that about 25 percent of patients who have  
20 prior thrombosis will develop recurrent thrombosis.  
21 So not only is there a high prevalence of post  
22 phlebitic syndrome, a condition that's clinically  
23 indistinguishable from recurrence, but these patients  
24 are also susceptible to recurrence.

25 And the final sort of piece to the puzzle

1 is that once these patients have had venous thrombosis  
2 and their physicians are aware of that diagnosis, they  
3 often have a heightened awareness of the disease  
4 itself and will present themselves more frequently and  
5 in a more timely fashion than patients without  
6 previous venous thrombosis.

7 So I think all of those factors underline  
8 the frequency of the problem.

9 Now, as with any problem with venous  
10 thrombosis, there's a danger in sending patients home  
11 who have the disease because we know that about half  
12 of them will come back with fatal or nonfatal  
13 pulmonary embolism. So we don't want to miss those  
14 who have disease.

15 On the other hand, we don't want to over  
16 diagnose because, as was pointed out previously, the  
17 treatment, which invariably is anticoagulant therapy,  
18 is associated with a significant incidence of adverse  
19 experiences, about seven percent over one year and  
20 then about two percent per year, and then there's the  
21 inconvenience of taking a pill every day and going for  
22 monitoring, and so on, and being labeled as somebody  
23 who is thrombophyliaic.

24 So you don't want to over diagnose, and  
25 you don't want to under diagnose. What do we do

1 currently?

2 Well, what we do currently is a whole  
3 mishmash of things, and in fact, whereas we have  
4 terrific diagnostic algorithms for virgin patients who  
5 have never had previous venous thrombosis, serial  
6 ultrasound, serial IPG, venography, all of those are  
7 validated approaches. There is no approach that is  
8 currently available to the diagnosis of suspected  
9 recurrent DVT that has been validated by management  
10 trial.

11 The best test historically has been  
12 radioactive fibrinogen uptake scanning, which has a  
13 number of limitations and is now no longer available.

14 Similar to apcitide, it's a  
15 radiopharmaceutical and is a physiological test, but  
16 the down side with it is that it's derived from human  
17 products and has potential viral transmission and, as  
18 well, you have to wait 12 to 24 hours before you get  
19 an answer, and you don't want to do that in this  
20 disease. You want to make a diagnosis, get the  
21 treatment started, or send the patient home in a  
22 timely fashion.

23 Apcitide has the potential to overcome  
24 both of those limitations. It's not a human derived  
25 product, and you can get an answer within two hours at

1 the most.

2 Now, what do you and I care about  
3 clinically? When you look at accuracy data and  
4 agreement data, you say, "Well, that's very nice, but  
5 what we care about is can we make decisions based on  
6 the results of the accuracy indices."

7 And the most valuable characteristic of a  
8 test for venous thrombosis is its sensitivity because  
9 the sensitivity has a profound impact on the negative  
10 predictive value.

11 And our best estimate of sensitivity in  
12 this study, and I think probably the red column  
13 represents the best estimate because these are  
14 patients who presented within days of onset of  
15 symptoms, and keep in mind this is probably somewhat  
16 of a conservative estimate, in other words an under  
17 estimate of true sensitivity of apcitide.

18 This estimate of around 85 percent  
19 sensitivity, and this includes both calf DVT and  
20 proximal DVT, is very consistent with tests, such as  
21 venous ultrasonography, which as was previously shown  
22 has a sensitivity of around 80 to 90 percent for the  
23 combination of calf and proximal DVT, and is certainly  
24 favorable when compared with impedance  
25 plethysmography, which has a sensitivity that's even

1 lower than that, probably in the 75 to 80 percent  
2 range, when calf DVT is pooled together with proximal  
3 vein thrombosis.

4 So this sensitivity is in the range of  
5 something that I would consider to be extremely  
6 useful, particularly when we're so desperate in  
7 patients with previous disease, and we need all of the  
8 information that we can get.

9 So if you gave me this test tomorrow with  
10 these accuracy indices, I would be happy to use it and  
11 say this is probably as good a test as we've got in  
12 recurrent disease, and I may use it alone, but more  
13 likely I would use it in conjunction with other  
14 information, pretest probability, venous  
15 ultrasonography, and perhaps other tests that are  
16 available to me.

17 And that's what we're left with in  
18 patients with previous disease. We often make a  
19 decision based upon a number of different test  
20 results.

21 Finally, a quick comment about the  
22 specificity. Again, I think what this says is that  
23 the specificity is around 70 percent, which doesn't  
24 provide us with a high enough positive predictive  
25 value to be diagnostic of venous thrombosis when the

1 test is abnormal, but I think the important message is  
2 that the prevalence of a normal test is going to be  
3 high enough to make the test useful.

4 So in my opinion, if I was to have this  
5 test tomorrow, what I would say is I would take  
6 patients with previous disease, do the test, and if  
7 the test result is negative, I would be reasonably  
8 comfortable sending the patient home without  
9 anticoagulant therapy.

10 I turn the floor back over to Dr. Dean.

11 DR. DEAN: Thank you, Dr. Ginsberg.

12 Now, one of the questions that was brought  
13 up and was alluded to by Dr. Sostman was in regard to  
14 radiolabeled platelets. Radiolabeled platelets  
15 performed well, except in cases where the patient was  
16 undergoing anticoagulation. So the question is: how  
17 does AcuTect perform in the presence of  
18 anticoagulants?

19 In this particular data chart, the  
20 agreement rate was with the institutionally read  
21 venogram, and as you can see here, the data are  
22 consistent with there being no effective  
23 anticoagulants as indicated on the agreement rate of  
24 AcuTect.

25 Now, one of the things we would like to

1 address because I believe it will be the subject of  
2 discussion later is the risk of potential bias in,  
3 quote, unquote, post hoc analysis.

4 There are three points we'd like to make  
5 here. One is that this is a methodological problem.  
6 This was a search for truth. We thought we had it.  
7 It was obvious we didn't, and we had to find it.

8 So one way or the other, this data wasn't  
9 going to be useful until we found truth.

10 The second thing I want to bring your  
11 attention to is that you saw that Hamilton produces  
12 the best measure of truth, and they were blinded to  
13 the clinical end AcuTect results.

14 In addition, as mentioned by Dr.  
15 Gottschalk, the AcuTect images were not the subject of  
16 a retest. That's like you've collected the clinical  
17 test sample, and the clinical test sample was  
18 collected according to protocol. So the integrity of  
19 that is maintained.

20 And the last point is that, of course, the  
21 prevalence of the disease is consistent with the  
22 published results.

23 So in summary, what you've seen today is  
24 that the blind read venography, as evidenced by Study  
25 B, was flawed by an unexpectedly high positivity.

1 Hamilton blind read validates the consistency of the  
2 study populations as is expected from the demographics  
3 in the presenting signs and symptoms, and the  
4 performance of AcuTect.

5 Based on the Hamilton blind read, AcuTect  
6 would meet the efficacy criteria, and the Hamilton  
7 blind read, importantly, is a treatment validated  
8 reading criteria that has been used in pivotal studies  
9 for the FDA approval of Lovenox and Normiflo, again,  
10 products for the treatment of DVT.

11 So you can see how we would conclude that  
12 AcuTect is safe and effective for the diagnosis of  
13 acute deep vein thrombosis, venous thrombosis, and we  
14 would ask that you consider and recommend approval for  
15 this indication.

16 Okay. I would now like to introduce Dr.  
17 Raymond Taillefer, who will present his findings in  
18 his clinical study with the agent. Dr. Taillefer has  
19 done over 40 patients with AcuTect and will comment on  
20 the performance of AcuTect in his hands.

21 DR. TAILLEFER: Thank you.

22 Good morning. Since my time is already  
23 up, I'll be very brief.

24 (Laughter.0

25 DR. TAILLEFER: I'm Raymond Taillefer.

1 I'm professor of nuclear medicine and radiology, and  
2 I'm also the Director of Research and Nuclear Medicine  
3 at the Hospital Hotel Dieu de Montreal, and I, as  
4 pointed out by my colleague, I was involved as an  
5 active clinical investigator in that project, and I  
6 would like to share with you some data that we have  
7 and some images.

8 Before I will show you a few images,  
9 detection of acute venous thrombosis with AcuTect, I  
10 would like to show you some data on the  
11 biodistribution of this compound which is relevant to  
12 what we can discuss as far as the imaging is  
13 concerned.

14 So the first thing that we should know  
15 about this product is that the major pathway of  
16 excretion is through the kidneys, and in fact, close  
17 to 90 percent of the injected dose will be excreted  
18 through the kidneys over 24 hours after injection, and  
19 about 50 percent after two hours following the  
20 administration.

21 The hepatobiliary excretion will be  
22 approximately six to ten percent over 24 hours, and  
23 obviously the organs which will show the excretion of  
24 this tracer will be significantly seen and very  
25 rapidly seen after the injection.

1           For those of you who are interested in  
2 radiation dosimetry, the main effective dose  
3 equivalent is 0.034 grams per millicurie, which is  
4 basically similar to what we have in standard clinical  
5 nuclear medicine for different agents and different  
6 regular tracers that we use in daily practice.

7           The maximum organ absorbed dose will be  
8 the urinary bladder wall with .22 rads per millicurie,  
9 and this is why we can inject up to 25 millicuries per  
10 patient.

11           And the estimated biological half-life of  
12 AcuTect is 1.9 hours with a mean half-life in the  
13 plasma of approximately one to 1.7 hours.

14           Now I would like to show you whole body  
15 distribution data performed in normal volunteers, and  
16 as you can see, these images are whole body images  
17 performed in the anterior view, posterior view, ten  
18 minutes after the injection of AcuTect, 60 minutes,  
19 and then four hours after the injection.

20           So very soon, very early after the  
21 injection of AcuTect, intravenous injection, we can  
22 see that we have an increased uptake in the liver and  
23 also the kidneys, and in posterior view you can see  
24 the increased kidneys' activity and also urethral  
25 activity, and of course, bladder, urinary bladder

1 increased uptake. So this will be seen ten minutes  
2 after the injection.

3 Then 60 minutes later, you will start  
4 seeing a slightly decreased liver activity and  
5 increased gall bladder retention and excretion and the  
6 same thing for the kidneys and bladders, which are  
7 very well seen on the 60 minute images.

8 Of course, because of the half-life in the  
9 blood, which is approximately one to 1.5, 1.7 hours,  
10 we will see cardiac chambers. Here's the blood  
11 activity in the cardiac area here which is normal, and  
12 then this uptake will slightly decrease and then over  
13 at four hours after the injection this activity has  
14 significantly decreased, but we still have some gall  
15 bladder activity and also some kidney and urinary  
16 bladder uptake.

17 Now, if we pay attention the lower limbs  
18 because this is the region of interest for us in  
19 clinical practice, then I did the same thing. So we  
20 have images performed at ten minutes after the  
21 injection, 60 minutes, and two hours after the  
22 injection. We have the anterior thigh, anterior  
23 knees, and anterior calf view, and the same thing for  
24 posterior pelvis, posterior knees, and poster calves.

25 And as you can see we have, at ten minutes

1 after the injection, we still have some activity in  
2 the blood pool, again, because of the half-life, and  
3 in patients when we pay attention to the posterior  
4 knees area, we can see that there is a slight  
5 increased uptake, linear uptake, responding to the  
6 popliteal vein, and this is a normal finding when we  
7 have symmetrical uptake, and this is because the  
8 popliteal veins are more superficial, and this is why  
9 we can clearly see them on the posterior view.

10 Also, in some patients we might see the  
11 distal part of the popliteal vein and in some patients  
12 also we can see the proximal part of the tibial and  
13 peroneal veins.

14 At 60 minutes this activity in the  
15 popliteal area will slightly decrease over time. So  
16 if we draw a sketch, a scheme from the activity from  
17 this popliteal region over time, you will see a  
18 decrease over time of the activity, but in many  
19 patients we will see a slightly increased uptake in  
20 the joint, which corresponds to a synovial uptake that  
21 we see with all types of antibodies and also different  
22 peptides, which is normal findings, and we must not  
23 confuse that with superficial or deep vein thrombosis.

24 But, again, as you can see, this activity  
25 slightly decreases over time, and then at two hours

1 after the injection we don't see anymore significant  
2 increased uptake in the popliteal region. So this is  
3 a normal finding. So we don't see any significant  
4 increased uptake.

5 We always compare both limbs to each  
6 other, and there is no activity also in the thighs.

7 Another negative case, so again it's very  
8 important to always compare each side, and we do it  
9 systematically, both anterior and posterior views, in  
10 order to make sure that we are comparing exactly the  
11 same segments of the veins.

12 So this is a case, an obviously positive  
13 case in a patient who had been treated with  
14 anticoagulant therapy, with heparin for two days  
15 before the patient was enrolled in that study, and as  
16 you can see here, although the patient was under  
17 anticoagulant therapy, we can clearly see on these  
18 anterior views and posterior views performed 60  
19 minutes after the injection, we can clearly see this  
20 increased uptake, which is quite linear, relatively  
21 intense, and corresponds to the pathway of deep vein.

22 In this case, these veins were the tibial  
23 ones. So posterior and anterior tibial veins, which  
24 show a very significantly increased uptake, and it's  
25 very important, again, to compare to the other limb,

1 but also to make sure that this uptake corresponds to  
2 a deep vein and not to a superficial vein. In this  
3 case, this is quite obvious, and again, this patient  
4 was under anticoagulant therapy for two days before  
5 getting demonstration with AcuTect.

6 Another patient with also a deep vein  
7 thrombosis involving in this case the right leg, which  
8 is well seen on the anterior view. In this case, the  
9 images have been obtained tow hours after the  
10 injection. So this is not the deep vein thrombosis.  
11 This corresponds to a urinary catheter. So this is  
12 why it's very, very hard.

13 But then we don't see any significantly  
14 increased uptake in the thigh, neither in the knees.  
15 This is normal uptake in the knee joint, but here we  
16 have this increased uptake corresponding to the deep  
17 vein thrombosis, which is very well giving aid to this  
18 patient.

19 Now, in some patients we can also see both  
20 superficial and deep vein thrombosis at the same time,  
21 and this is an example. Again, the same pattern: ten  
22 minute, 60 minute, and two hours after the injection,  
23 and if you pay attention to this image here, this is  
24 an image of the posterior calf obtained two hours  
25 after the injection. We can see that there is a

1 slight increased uptake, a linear uptake, which  
2 corresponds to a superficial vein, and in this case  
3 this patient had also superficial vein thrombosis,  
4 plus in the popliteal region we have this increased  
5 uptake corresponding to a deep vein thrombosis of both  
6 calf, popliteal region, and also the distal part of  
7 the right thigh.

8 So with this patient we had both  
9 superficial and deep vein thrombosis.

10 Now, as pointed out by my colleagues  
11 previously, post phlebitic syndrome is a real clinical  
12 problem and a real puzzle in clinical practice, and  
13 this is a case of a patient who was admitted for  
14 recurrent episodes of possibly deep vein thrombosis.  
15 This patient had a prior history of deep vein  
16 thrombosis on the right leg a few years before we did  
17 the study, and this patient was complaining of  
18 recurrent symptoms, especially a slight edema, and we  
19 did the study in this patient at ten minutes, 60  
20 minutes, and two hours, exactly the same way we did  
21 for the previous patients.

22 And as you can see in this patient on the  
23 anterior view, we have this slightly diffused increase  
24 uptake in the soft tissues on the right extremity that  
25 we can see on the posterior view, but at no time we

1 are able to recognize that there is a linear uptake  
2 corresponding to a deep vein pathway.

3 So in this case when we have this kind of  
4 slightly increased diffused uptake involving the soft  
5 tissue, we have two options. It can be either related  
6 to venous insufficiency or lymph edema.

7 So in this case a follow-up study showed  
8 that it was not a recurrent episode of DVT, but just  
9 a post phlebitic syndrome with inflammation, and this  
10 patient was treated with anti-inflammatory medication,  
11 but as detected here, we didn't see any significant  
12 signs of deep vein thrombosis, and this patient was  
13 not treated for deep vein thrombosis, but just for  
14 inflammatory reaction.

15 The same thing in another patient with  
16 similar history, but in this case we have similar  
17 uptake in all the segments. So we cannot recognize  
18 any increased uptake corresponding to a linear deep  
19 vein thrombosis, and this patient was treated for post  
20 phlebitic syndrome without deep vein thrombosis.

21 Also it's important as pointed out by Dr.  
22 Ginsberg to detect previous -- not previous -- but  
23 acute deep vein thrombosis in patients with post  
24 phlebitic syndrome, and this is a case of a patient  
25 having prior history of deep vein thrombosis. The

1 patient came back and now we can see that there is an  
2 increased uptake, linear uptake, corresponding to a  
3 deep vein thrombosis in the patient with recurrent  
4 symptoms of deep vein thrombosis.

5 DR. DEAN: Thank you, Dr. Taillefer.

6 And for a brief final comment I'd like to  
7 introduce Dr. Michael Bettman, Chief of Cardiovascular  
8 Interventional Radiology at Dartmouth.

9 Thanks.

10 DR. BETTMAN: I appreciate the opportunity  
11 to make some observations.

12 My involvement in this study has been  
13 essentially nonexistent. I have to confess to being  
14 one of the blind readers in Study A, I believe. I'm  
15 sure I was the one who was the most accurate.

16 (Laughter.)

17 DR. BETTMAN: But other than that, I have  
18 had no involvement in this.

19 I would like to just comment really on the  
20 nature of the disease and on the role of venography  
21 and of other diagnostic methods, and in my mind the  
22 necessity for the advantages of AcuTect.

23 First of all, as has been pointed out,  
24 deep vein thrombosis and pulmonary emboli are very  
25 common disease entities. They occur with great

1 frequency, and it's very clear from multiple studies  
2 that they are not diagnosable with any degree of  
3 accuracy from a clinical standpoint.

4 The clinical suspicion does play a very  
5 important role, but it is only that. It is a  
6 suspicion which should generate further tests.

7 The tests that are available for deep vein  
8 thrombosis have been outlined to you. There have been  
9 various radionuclide studies that have been tried over  
10 the years, none of which has really been entirely  
11 satisfactory, perhaps with the exception of the  
12 labeled fibrinogen studies, which had very high  
13 specificity, relatively low sensitivity -- I'm  
14 sorry -- very high sensitivity, very low or relatively  
15 low specificity, but is no longer available at any  
16 rate.

17 And venography has certainly been used for  
18 a long time, as has ultrasound and impedance  
19 plethysmography and several others.

20 What is the role of venography? Well,  
21 venography really ha fallen out of use with the advent  
22 particularly of ultrasound, and it's somewhat  
23 interesting because the accuracy of ultrasound overall  
24 has been shown in multiple tests to be somewhat  
25 fallible, at least compared to venography.

1                   Nonetheless, ultrasound is noninvasive,  
2                   has really no complications other than its lack of  
3                   accuracy and, therefore, has been widely utilized.  
4                   The big difficulty with ultrasound or the big  
5                   difficulties are, first, that it really is not  
6                   particularly accurate below the knee, and, secondly,  
7                   that it is dependent on a degree of expertise.

8                   Venography is a diagnostic modality that  
9                   I think has fallen probably for good reasons. It is  
10                  relatively invasive. It's relatively expensive to  
11                  perform. It does have a discrete incidence of  
12                  complications, of unwanted complications, and it is  
13                  also operator dependent.

14                  And I guess the question that I wanted to  
15                  address primarily is why was there the disagreement  
16                  between the blind reading of venography, on the one  
17                  hand, and, on the other side, the readings at Hamilton  
18                  and the reading at the institutions.

19                  The reasons, I think, are based in the  
20                  utilization of venography. Venography, as I said, is  
21                  dependent on a degree of experience. It requires  
22                  assiduous attention to detail in order to be accurate,  
23                  and that means very careful needle placement, very  
24                  careful fluoroscopic evaluation as the contrast is  
25                  infused, very careful obtaining of films while there's

1 good contrast filling.

2 In theory, it's not at all difficult, but  
3 in practice if you don't do it with some frequency,  
4 it's really just not done well, and that, I think,  
5 leads to two problems.

6 One is in the performance and the other is  
7 in the interpretation. I think as these studies were  
8 performed at the site in all likelihood a fair amount  
9 of information was gained from the clinical setting  
10 and from the fluoroscopic observation and not from the  
11 films. Because of the lack of great utilization of  
12 venography, I think it's likely that the films  
13 obtained at the different sites were really not  
14 entirely optimal. That's one side of the equation.

15 The other side of the equation is why were  
16 the blind readings not more accurate. Why did they  
17 agree to a greater extent with the readings at the  
18 site?

19 And I think the reasons, again, are  
20 related to experience. Since people are not doing  
21 venograms with any great frequency, are not used to  
22 techniques, and are not used to very careful  
23 evaluation, I think that it's logical to assume that  
24 the accuracy would be somewhat lower than it would  
25 have been a few years ago when venograms were done

1 with great frequency.

2 So in summary, I think that AcuTect is a  
3 diagnostic test that is needed in this day and age for  
4 a common and important disease. I think that there  
5 was clearly a disagreement between the blind readers  
6 and the on-site reading in the Hamilton readers. I  
7 think that is really clearly understandable and  
8 probably should not be heavily taken into  
9 consideration when considering the safety and efficacy  
10 of AcuTect.

11 Thanks for your attention.

12 MR. PIPER: That concludes our formal  
13 presentation. Sorry for going a little bit beyond our  
14 allotted time, but we'd certainly like to entertain  
15 questions if you have them now.

16 CHAIRPERSON RAMSEY: Thank you very much.

17 I think looking at the program and the  
18 time allotted, I'd like to say let's take a break now,  
19 a 15 minute break, and we will then begin again.  
20 Let's see. It's five minutes after. At 20 minutes  
21 after ten with the question.

22 So if the committee could please hold  
23 their questions, and we thank you very much for your  
24 presentation.

25 (Whereupon, the foregoing matter went off

1 the record at 10:02 a.m. and went back on  
2 the record at 10:22 a.m.)

3 CHAIRPERSON RAMSEY: We'll now be starting  
4 the session for the Committee questions on the  
5 sponsor's presentation. I want to thank the sponsor  
6 for their presentation this morning and the Committee  
7 members, again, for all being here today.

8 And are you prepared?

9 I know there are a few questions. Dr.  
10 Links, would you like to go first? You had a question  
11 earlier.

12 DR. LINKS: I have three related  
13 questions. All in a way involve contrast venography.  
14 The first is: what studies, if any, have ever been  
15 done to determine the accuracy of venography in  
16 diagnosing DVT?

17 The second is has venography been used in  
18 the past as a, in quotes, gold standard to assess the  
19 diagnostic performance of any other test, for example,  
20 ultrasound?

21 And then the third question is: if  
22 venography is the gold standard in this particular  
23 trial and the indication is for acute venous  
24 thrombosis, what's the evidence that would tie the  
25 indication to the results of the clinical trial,

1 specifically highlighting the word "acute"?

2 DR. DEAN: Okay. For the first part of  
3 that question I'd like to ask Dr. Ginsberg to comment,  
4 and that's in regard to the, as I understand it,  
5 validating venography as a true standard.

6 DR. GINSBERG: Yeah. I can actually try  
7 and knock off the first two questions, if that's okay.

8 With regards to accuracy of venography,  
9 that was tested in a prospective management study in  
10 which patients with a normal venogram were discharged  
11 home and followed up. So they presented with the  
12 suspicion of DVT, had a venogram. If the test result  
13 was normal, then they were followed up for I think it  
14 was six months to a year for the absence of venous  
15 thromboembolic events, and there were about 150  
16 patients who had such findings, and I think one  
17 percent returned with objectively confirmed venous  
18 thromboembolism.

19 So that supports the negative predictive  
20 value of venography.

21 With respect to comparing other  
22 noninvasive tests, there's an excellent study that was  
23 done by Tom Lensing and published in the New England  
24 Journal in 1989 in which what Dr. Lensing did was he  
25 systematically performed compression ultrasound and

1 venography on all patients who presented with the  
2 suspicion of DVT and showed that the sensitivity of  
3 ultrasound for proximal vein thrombosis was over 90  
4 percent and of calf DVT was less than 50 percent, and  
5 that the specificity was around, I think, in the 96  
6 percent range.

7 So certainly in that study, which was done  
8 in a single center, and incidentally, the Dutch group  
9 used very similar criteria to the ones that we used,  
10 that we have used and that we use in this study, I  
11 think is the best evidence supporting the test.

12 There's also a similar study done with IPG  
13 and leg scanning comparing it with venography as a  
14 reference standard. It was done very similarly and  
15 validated that as a substitute for venography.

16 DR. LINKS: Don't go away because as long  
17 as you're up there, before we get to the other  
18 question I have a clarification on something you  
19 presented.

20 It was stated that there were potential  
21 problems with both the performance and the  
22 interpretation of the venogram, and obviously you all  
23 could only address a reinterpretation, not a  
24 reperformance, so to speak.

25 What did you do to assess the technical

1 quality of the venogram, and did you throw out any  
2 patients because you said the venogram was not  
3 technically acceptable?

4 DR. GINSBERG: Yes, we did. So if the  
5 venogram was unacceptable, for example, if the -- not  
6 only if the veins were not visualized, but if there  
7 was a very hazy film and we weren't able to get clear  
8 visualization of important areas of the deep veins, we  
9 did not -- we considered those inadequate or  
10 indeterminate.

11 DR. LINKS: And were all indeterminate  
12 reads for whatever reason thrown out of the study in  
13 the clinical results based on Hamilton?

14 DR. GINSBERG: My understanding -- well,  
15 sorry, Dean.

16 DR. DEAN: I should step in here because  
17 Hamilton only knew -- Hamilton only saw films, and  
18 they recorded things on a piece of paper. So he  
19 doesn't know what happened to the data.

20 (Laughter.)

21 DR. DEAN: So I'd like to ask a  
22 statistician who was responsible for that to address  
23 that point.

24 DR. MADSEN: Whatever was used as truth in  
25 the Hamilton read case, yes, at all the regions, if

1 the whole set of scans were determined to be  
2 indeterminate, that case was one of our unevaluable  
3 cases, but if an individual region was indeterminate,  
4 that region wasn't included in the assessment.

5 DR. KONSTAM: Sorry. What was the number  
6 of unevaluable cases at the end?

7 DR. MADSEN: Altogether for each study we  
8 had -- on the basis of indeterminate reads, we  
9 probably had ten or 11, I guess.

10 How many? Nine, nine altogether.

11 MR. MADOO: Could you please provide your  
12 name, please?

13 DR. MADSEN: Sorry. Kathleen Madsen.

14 DR. LINKS: So back to acute versus  
15 chronic.

16 DR. DEAN: Acute versus chronic. I'm  
17 going to ask Dr. Sostman to comment on the data as it  
18 relates to the response.

19 DR. SOSTMAN: Well, first of all, I'm not  
20 100 percent sure I understood the question. So I'll  
21 try to give you my answer as I interpret it.

22 In the first place, it's my understanding  
23 from Dr. Ginsberg's presentation that the Hamilton  
24 readers used their criteria for acute DVT as a  
25 positive test, and he's shaking his head yes.

1           Secondly, not actually related to the  
2 venogram, but to the results of the apcitide study, if  
3 you remember that slide where they looked at the  
4 subgroup analysis and as the subgroup went to a more  
5 acute clinical presentation, that is, less than three  
6 days from the onset of signs and symptoms, the  
7 sensitivity of the test went up, and that, I think, is  
8 quite consistent with the rationale for the test,  
9 which is binding of the agent to activated platelet  
10 receptors.

11           So that to me is what makes this  
12 specifically an acute thrombus agent.

13           Does that answer your question?

14           DR. LINKS: Thank you.

15           DR. DEAN: Thank you, Dr. Sostman.

16           CHAIRPERSON RAMSEY: Questions?

17           Could you just state your name and then  
18 ask your question?

19           DR. D'AGOSTINO: Ralph D'Agostino.

20           I have some questions go to the  
21 statistical issues, and I'd like to ask, first of all,  
22 so that I can understand the context of the studies  
23 where the 60 percent comes from, and in your  
24 presentation you said 75 percent, but the statistical  
25 analysis, if I understand it correctly, would have

1       been really testing the 60 percent agreement rate.

2                    Could you clarify why the 60 percent and  
3       is it really a one tailed test for the 60 percent  
4       rate?

5                    DR. DEAN:        I'm going to ask my  
6       statistician to come up and respond to that again,  
7       Kathleen Madsen.

8                    DR. MADSEN:  I knew this was going to come  
9       up.  You know, the 75 percent -- well, in the design  
10      piece studies, we were required to justify that the  
11      studies were being designed with adequate statistical  
12      power, 80 percent, and with adequate numbers of  
13      patients to establish this expected rate of 75  
14      percent.

15                   The approach we chose was to take a  
16      confidence interval approach for establishing that  
17      studies were adequate in terms of power and sample  
18      size for establishing that the true rate was not less  
19      than 75 percent by more than 15 percent.  That was the  
20      confidence which translates to a 60 percent lower  
21      bound on the confidence interval.

22                   One sided because we're not concerned that  
23      it would be different from 75 percent in a positive  
24      way; on in the negative side.  So we saw it as a one  
25      sided hypothesis test.

1 DR. D'AGOSTINO: But it is then basically  
2 a test of agreement equals 60 percent versus agreement  
3 greater than 60 percent that we're actually looking  
4 at, not 75?

5 DR. MADSEN: Well, I think what we have in  
6 this study design is -- yes, we're looking to estimate  
7 agreement rate, and what we're trying to establish is  
8 that the lower bound of the confidence interval, one  
9 side confidence interval, for that agreement rate is  
10 not less than 60 percent. So it's tied to the lower  
11 bound. It's not tied to the point estimate itself.

12 DR. D'AGOSTINO: I have two other  
13 questions. One, in terms of interpreting the  
14 statistics that we have before us, if I heard the  
15 discussion correctly or the presentation correctly,  
16 the analogy was if you find your assays are wrong, you  
17 go and get a better assay or you go and get a correct  
18 one so then you can believe your data. So that's one  
19 way of looking at the data, that somehow or other we  
20 didn't have the correct answer to begin with.

21 Another way of looking at the data is that  
22 I'm in the situation often where you run your  
23 statistical hypothesis test, you run your confidence  
24 intervals, and you find out that you don't meet the  
25 criteria, that your study is not positive, and then

1 you say, "Gee, I wonder why. The blind's broken.  
2 I've done my primary analysis," and then you go and  
3 you say, "My God, some of the individuals who were in  
4 the analysis really shouldn't belong there. They were  
5 protocol violators," and then I redo the analysis,  
6 and, lo and behold, the analysis is now positive.

7 And how do we as a group interpret the  
8 fact that you did the primary analysis, it didn't work  
9 for you, and you did a secondary analysis and it did  
10 work? What are the levels of significance? What is  
11 the interpretation from a statistics point of view?  
12 Leave the clinical questions aside for the moment and  
13 let others address it.

14 But what is the statistics? How do I  
15 believe the second set of analyses?

16 DR. DEAN: We're going to have another one  
17 of our consultant statisticians, John Balser, address  
18 that.

19 DR. BALSER: Is this working?

20 Okay. If I understand the question  
21 correctly, the issue has essentially to do with what  
22 kind of adjustments might one want to apply in a case  
23 where we've done an additional analysis.

24 Typically that kind of adjustment is  
25 required if, in fact, you've got more than one

1 statistical test which is valid or potentially cases  
2 where you're looking at multiple endpoints and, you  
3 know, those kinds of situations.

4 DR. D'AGOSTINO: I'm not asking that. I'm  
5 asking: my analysis didn't work. I redefine -- I can  
6 say I'm redefining my data set, and now my analysis  
7 does work. How do I look at that?

8 DR. BALSER: Yeah, I understand what  
9 you're saying.

10 DR. D'AGOSTINO: It's not multiple  
11 testing.

12 DR. BALSER: You're talking about  
13 excluding certain data points from your analysis.

14 DR. D'AGOSTINO: No, I'm talking about my  
15 original analysis didn't work. I redefine my data,  
16 and now it does work. How do I -- I gave my -- the  
17 example I gave was as an example of protocol  
18 violators, but it's the second look at the data, and  
19 that's the question I'm really asking.

20 How do I look at that in a statistics  
21 point of view? What we'd like to see is you've done  
22 a study and you get replication or you have two  
23 studies that replicate each other.

24 Here we have one study that was positive.  
25 We have another study that was negative, but then it

1 becomes positive if I redefine -- basically redefine  
2 my endpoint.

3 DR. BALSER: We're not redefining our  
4 endpoint. Our endpoint is still AcuTect as the test.  
5 We are redefining, if you will, the gold standard.  
6 The gold standard was an inappropriate standard to be  
7 using. It invalidates the test entirely, and that's  
8 really the point.

9 We're not doing multiple testing. We're  
10 not saying that we're doing another test on the same  
11 data and somehow, you know --

12 DR. D'AGOSTINO: Well, but your gold  
13 standard was by the blinded readers and now you have  
14 Hamilton reading. We'll pick that up later on with  
15 the FDA and maybe come back.

16 But let me ask one other question. When  
17 you give the analysis, you do it on the aggregate  
18 reads from each of the blind readers as opposed to  
19 individual readers. Was the protocol said to do the  
20 majority?

21 DR. BALSER: Are you talking about the  
22 aggregate for the AcuTect readers or are you talking  
23 about the majority blind read?

24 DR. D'AGOSTINO: In the analysis that was  
25 presented looking at the AcuTect versus Hamilton

1 versus the CV, it was only for the aggregate that I  
2 seem to recall you presenting as opposed to the  
3 individual readers.

4 DR. BALSER: No, we actually did present  
5 the individual reader results for AcuTect, each of the  
6 individual readers, as well as the aggregate.

7 DR. D'AGOSTINO: What should I be looking  
8 at?

9 DR. BALSER: Well, prospectively in the  
10 protocol each individual reader was, in fact, to be  
11 looked at. I believe that aggregate came up somewhat  
12 later, possibly in discussions as to how to simplify  
13 the presentation.

14 DR. D'AGOSTINO: So I should look at the  
15 individual readers. So it's three out of six in the  
16 first study and six out of six in the second.

17 DR. BALSER: For Hamilton I think it was  
18 somewhat better than that, but essentially, yes, the  
19 individual readers should be looked at.

20 DR. D'AGOSTINO: Thank you.

21 CHAIRPERSON RAMSEY: Other questions?

22 Dr. Ponto.

23 DR. PONTO: I have two questions. The  
24 first is we've talked about we have an imperfect gold  
25 standard here, and that maybe our best gold standard

1 would be outcome. Did you look at outcome in any of  
2 these patients?

3 And my reading of the documents, the  
4 majority of these patients were treated as if they had  
5 DVT, correct?

6 DR. DEAN: Okay. I'm going to refer that  
7 to Dr. Nicodemus, who's our clinical operations head.

8 DR. NICODEMUS: Yes. Two questions. The  
9 endpoint for the study was, in fact, the results of  
10 the comparison. So an outcomes study was not  
11 conducted with these patients formally.

12 The second question -- actually remind me  
13 of the second question.

14 DR. PONTO: The majority of the patients  
15 were actually treated like they had DVT.

16 DR. NICODEMUS: Right. The actual patient  
17 treatment data reflects the treatment. About 70  
18 percent of the patients received some form of  
19 anticoagulation in the study. That reflects patients  
20 receiving anticoagulation at the time of their  
21 diagnostic evaluation. In some circumstances patients  
22 were actually anticoagulated during the work-up as  
23 part of the rule out process.

24 The actual data for the number of patients  
25 who received longstanding anticoagulation is not part

1 of the analysis, but would be less than 70 percent.  
2 It would be probably closer to 50 percent.

3 DR. PONTO: I have a second question. The  
4 FDA provided us with the individual AcuTect readings,  
5 and we've talked a lot about the agreement rates  
6 between the Hamilton read, the blind read, and all of  
7 that. What about the agreement between the AcuTect  
8 reads? Can you give us some insight into that?

9 DR. DEAN: Okay. I'm going to ask one of  
10 my statisticians to respond to that.

11 DR. MADSEN: In terms of kappa statistics  
12 among individual blind readers, they were pretty low.  
13 So if you just compared pairs of readers, you would  
14 see the kappa statistics that were, you know,  
15 generally less than .4, and that's considered a pretty  
16 low kappa statistic.

17 So -- but there was -- we also provided a  
18 measure of unanimity among readers, and I think you  
19 saw on the order of, you know, 60, 60 percent of the  
20 time they were unanimous in their readings of the  
21 images.

22 So the kappa statistic was low.

23 CHAIRPERSON RAMSEY: Dr. Konstam.

24 DR. KONSTAM: I'd like to ask three  
25 questions. The first is of any of the sponsor's

1 speakers.

2 In acute venous thrombus, I assume we can  
3 get to a point where the vein is actually occluded or  
4 nearly occluded or at least the flow is diminished,  
5 and that can be acute.

6 And I wonder what you feel that might --  
7 how that might impact on the diagnostic ability of  
8 AcuTect vis-a-vis delivery to the thrombus or the  
9 entire thrombus. Is that a problem?

10 DR. DEAN: That's a good question. Having  
11 worked with both antibodies and small peptides, we  
12 have seen at least in the clinical images some  
13 differences. Whereas antibodies would often light up  
14 the tip of a thrombus, these seem to diffuse right  
15 into the matrix quite readily so that we see the  
16 entire line light up, as you've seen the images.

17 So, you know, unless you strip out the  
18 veins and actually look at a cross-section and  
19 everything, you can't get a definitive answer, but --

20 DR. KONSTAM: Do you have any information  
21 from your animal studies to shed light on this  
22 particular question of what happens when the vein  
23 actually reaches a point of near occlusion?

24 DR. DEAN: Sure. Let me ask Dr. Lister-  
25 James if he can respond to that.

1 DR. LISTER-JAMES: In the animal studies  
2 I don't think any of the animals that we studied had  
3 totally occlusive thrombi, and so we weren't able to  
4 address that, but I think, as Dr. Dean mentioned, we  
5 have a small, highly diffusible tracer, and even if  
6 that weren't to be the case, then one would be able to  
7 pick up the ends of the thrombus.

8 DR. KONSTAM: Okay. My second question  
9 just gets back to this 60 percent or 75 percent figure  
10 that Dr. D'Agostino was asking about. I mean, where  
11 does that come from, either number, 60 percent or 70  
12 percent, in terms of agreement? Is there some  
13 precedent to that type of analysis and that level of  
14 accuracy as a gold standard?

15 DR. DEAN: I'm going to defer to one of my  
16 team members to address that.

17 DR. KONSTAM: I mean, 60 percent would  
18 mean ten percent better than a coin.

19 DR. DEAN: Right, right. One of the  
20 things you have to -- and I'll allow Dr. Nicodemus to  
21 expound on this -- but one of the things you have to  
22 understand is there are going to be successive factors  
23 that lower the potential agreement rate between the  
24 two tests, as you've seen. So we felt that that,  
25 based on prior history with this tracer, that 75

1 percent was a good target.

2 Dr. Nicodemus, do you want to comment  
3 further on that?

4 DR. NICODEMUS: Right. We have a number  
5 of references from the literature, a Lensing paper,  
6 and others that we can provide you and are in the  
7 briefing documents in which the agreement rates  
8 between blind read venographers -- and this was the  
9 basis of this calculation. If you take venography,  
10 conduct the reads blindly, and look at the agreement  
11 rates between venographers, the agreement rates in  
12 those reference papers is on the order of about 75  
13 percent.

14 That's similar with the agreement rate  
15 that was seen, for example, between the institutional  
16 read and the Hamilton read, 75 percent. So that was  
17 the basis for that intended endpoint, and then, again,  
18 as Dr. Madsen commented, when one's looking for a 75  
19 percent agreement rate, one has to keep in mind the  
20 confidence interval that one gets, and it's the lower  
21 limit of the confidence interval that reflects the 60  
22 percent.

23 So really 70 percent, 75 percent agreement  
24 would be what one would expect in the circumstance of  
25 a blind read exercise. This is different from the

1 clinical exercise. This is the constraints of reading  
2 the information without information. That was the  
3 basis.

4 DR. KONSTAM: Well, I guess I would just  
5 comment that even the 75 percent figure in terms of  
6 inter-observer or inter-observer variability with  
7 venography sounds very bad, and so it sounds like a  
8 bad state of affairs, and one would wonder whether,  
9 you know, that is sufficient to seek in a new agent,  
10 but I guess we'd have to think about that.

11 The third question, I'd like to ask Dr.  
12 Ginsberg something.

13 I guess I hear you say that based on the  
14 sensitivity figures that you see, and the number I  
15 remember is 70 percent range -- now, I know that in  
16 some subgroups it reached higher, but in the overall  
17 patient population, I think it was 70 percent or maybe  
18 slightly lower, and you commented that the sensitivity  
19 level that you saw might be adequate for you to say  
20 that if this test was negative, you'd be willing to  
21 send the patient home on the basis of that.

22 I think reflecting on that and reflecting  
23 also on the comment that the reason venography has  
24 some value in terms of outcome is that there are  
25 outcome studies that have been done that show that

1 patients with negative venograms are sent home and do  
2 okay by some standard.

3 I think based on those two points would  
4 you support a prospective study in which you took  
5 AcuTect, you pulled out patients who were negative,  
6 and you sent them home and followed them and sort of  
7 confirmed in an experimental trial that you were not  
8 harming patients by sending them home with a negative  
9 test?

10 DR. GINSBERG: Yeah, it's an excellent  
11 question. The sensitivity that I drew from the slide  
12 was closer to about 85 percent, and it's really  
13 critical that we get up between 80 and 90 percent.  
14 Otherwise you're too low, and your negative predictive  
15 value falls to levels that are too low to reliably  
16 make management decisions.

17 So what we're looking at really is this  
18 sensitivity here, which is probably --

19 CHAIRPERSON RAMSEY: Excuse me, Dr.  
20 Ginsberg. You have to speak into the microphone so  
21 that it goes on record. If you could use the pointer.

22 DR. GINSBERG: The pointer? Okay. We  
23 don't have a lot of high tech in Canada.

24 (Laughter.)

25 DR. GINSBERG: The sensitivity that I was

1 referring to, and keep in mind that I think this is a  
2 conservative sensitivity, but this would be  
3 approximately 85 percent, and the reason I use this  
4 group of patients is that these are patients whose  
5 onset is less than three days, in whom the venograms  
6 are likely to be the most accurate.

7 When we include all patients, we've got  
8 the background noise of the inaccuracy of  
9 interpretation of venography and the misinterpretation  
10 of venography.

11 In addition, the way the analysis was  
12 conducted was one that would be a conservative  
13 sensitivity. So, in fact, a sensitivity of 85 percent  
14 for both calf and proximal DVT would provide  
15 sufficient impetus for me to do a clinical management  
16 study.

17 Now, could this be a stand alone test? My  
18 thought would be that I would take patients according  
19 to their pretest probability, which is an important  
20 predictor of post test probability. If it was low and  
21 they had a normal P280, I'd send them home. If it was  
22 moderate and they had a normal P280, I'd probably also  
23 send them home, but if it was high and they had a  
24 normal P280, I'd probably use something else.

25 DR. KONSTAM: Well, I guess here's my

1 question. Taking that subgroup, say, as your new  
2 hypothesis, would you support a prospective study in  
3 patients with onset of symptoms less than three days  
4 who had a negative test and go forward and follow them  
5 and watch outcomes or whatever follow-up you would  
6 design? Would that be a study that you'd like to see?

7 DR. GINSBERG: Unquestionably, and we've  
8 done that with the D dimer assay, which has very  
9 similar accuracy indices, and which we and others have  
10 shown can be used to manage patients.

11 CHAIRPERSON RAMSEY: Thank you.

12 I'd like to just say to the Committee we'd  
13 like to end the question session at 11 o'clock and go  
14 forward with the next section. So with that in mind.

15 DR. AMENDOLA: I have a quick question.  
16 If we take the Hamilton read as the gold standard --

17 CHAIRPERSON RAMSEY: Could you state your  
18 name, please, again for the record?

19 DR. AMENDOLA: Dr. Amendola.

20 CHAIRPERSON RAMSEY: Thank you.

21 DR. AMENDOLA: If we take the Hamilton  
22 read as the gold standard, were the two positive and  
23 the two negative in the predictive bodies of AcuTect  
24 calculated?

25 DR. DEAN: Can Dr. Nicodemus? Dr.

1 Nicodemus, can you address that question?

2 DR. NICODEMUS: Actually can you repeat  
3 it? I wasn't quite certain of what you were saying.

4 DR. AMENDOLA: Right. If we take the  
5 Hamilton read as the gold standard, what were the true  
6 positive, true negative in predicted values of AcuTect  
7 calculated?

8 DR. NICODEMUS: The true positive and true  
9 negative in predictive values of AcuTect, actually the  
10 sensitivity slide that Dr. Ginsberg just showed was  
11 related to using Hamilton as the gold standard, and  
12 we'll see if we can -- in terms of true positives and  
13 true negatives from that, do we?

14 DR. GINSBERG: Basically sensitivity is a  
15 surrogate for true positives. So the true positivity  
16 rate would be in the sort of mid-80s. Specificity is  
17 a surrogate for true negative rate, and so the  
18 specificity would be about 70 percent, and then false  
19 positives can be calculated based on extrapolations  
20 from those data.

21 Is that the question you're asking?

22 DR. AMENDOLA: Right. I want to have some  
23 idea of what, you know, the accuracy of the test is  
24 and also the predictive value of the test if we take  
25 the Hamilton read as the gold standard.

1 DR. GINSBERG: I see. What you would need  
2 to do, as you know, is to set up a two-by-two  
3 contingency table based on the prevalence. I can tell  
4 you that with the sensitivity of 85 or 90 percent and  
5 a prevalence of around 30 percent and a specificity of  
6 around 70 percent, the negative predictive value would  
7 be in the range of 90 percent.

8 So, for example, with a prevalence of 30  
9 percent and a sensitivity of -- were are we here?

10 Okay. So these are the actual time  
11 points. So with prevalences of around we saw between  
12 26 and 30 percent, you can see the negative predictive  
13 value is slightly over 90 percent. The positive  
14 predictive value, not surprisingly, is in the range of  
15 about 50 percent, and obviously as it's well know, as  
16 the prevalence falls and reaches more contemporary  
17 figures of, say, 15 percent -- and this is why I say  
18 I'm comfortable using this test in clinical management  
19 studies -- is that if the prevalence is more  
20 realistic, 15 or 16 percent, the negative predictive  
21 value would be in the high 90s, which is as good as  
22 anything that we've got.

23 DR. AMENDOLA: Thank you.

24 CHAIRPERSON RAMSEY: Dr. Choyke.

25 DR. CHOYKE: Pete Choyke.

1 I think, you know, we'd all be happier if  
2 there were matched pairs that everybody could agree  
3 were negative and matched pairs where everybody could  
4 agree were positive, and what I'm wondering, and  
5 recognizing that there will always be gray cases where  
6 people will disagree and that's sort of in the more  
7 subtle cases; I'm wondering whether it's possible from  
8 either the first blind read or the Hamilton read to  
9 identify a subset of patients who all the readers  
10 agreed were negative and all the readers agreed were  
11 positive and look at how AcuTect did against those  
12 ends of the spectrum.

13 DR. DEAN: Dr. Nicodemus.

14 DR. NICODEMUS: Yeah, I don't have that  
15 specific analysis right now. I would point relative  
16 to the Hamilton, of course, you know, there is a  
17 unanimity of interpretation as the old standard, and  
18 for the AcuTect scans, as we mentioned, there's about  
19 a 60 percent unanimity rate, but the actual analysis  
20 you're talking about I don't have available for you  
21 right now. I'm sorry.

22 CHAIRPERSON RAMSEY: One more question.  
23 Dr. August.

24 DR. AUGUST: As we listen to these  
25 proceedings, there's a recurrence of three themes, and

1 that is the problems implicit with the fact that our  
2 gold standard is really not a gold standard, the  
3 problems relating to acute versus chronic  
4 thromboembolic disease, and then there is another one  
5 which we've talked less about, but is certainly here,  
6 the interaction of the therapies that patients were on  
7 with imaging results.

8           And it occurred to me as I was reading  
9 through the material prior to the meeting that with an  
10 appropriate animal model, one could really get a lot  
11 of insight into all of those three issues, and we've  
12 seen that there are data that we've been presented  
13 from animal models. Mostly they have to do with  
14 toxicity and maybe pharmacokinetics, and I'm just  
15 curious to know whether you have such data or if you  
16 don't, why don't we have it? Is it because the animal  
17 models really aren't relevant to the human situation  
18 or what?

19           But it seems to me that some of these --  
20 that the approach to answering some of these questions  
21 would be really admirably served by the use of an  
22 animal model.

23           DR. DEAN: I'm going to ask Dr. Lister-  
24 James to address that.

25           DR. LISTER-JAMES: I think the approach

1 that we took is we were most interested in the effect,  
2 of course, on the interaction of the product with  
3 human platelets, and that's why we did the study in  
4 vitro, looking at the binding of the agent or the  
5 ability of the agent to inhibit platelet aggregation  
6 in the presence or absence of heparin as a direct  
7 measurement of the effect of heparin on the ability of  
8 the product to bind platelets.

9 We did not do studies in dogs with or  
10 without heparin. I suppose one could do that study.  
11 Of course, one has to take into account the fact that  
12 the cross-reactivity of the agent with dog platelets  
13 is less than with human platelets. So that does tend  
14 to make it not quite as relevant as using human  
15 platelets.

16 So I think the real answer is that we  
17 chose to use the human -- as close to human situation  
18 as we could.

19 In terms of getting at acute versus  
20 chronic, that's particularly difficult to do in  
21 animals. As you're probably aware, dogs have a very  
22 highly developed fibrinolytic system. It's very  
23 difficult to develop chronic thrombi in the dog model  
24 or, in fact, in other models, and so we could not  
25 think of a way to address dealing with that

1 specificity issue in animals.

2 CHAIRPERSON RAMSEY: Very brief, please,  
3 Dr. Links.

4 DR. LINKS: A question of clarification.  
5 In looking through all of the data, obviously you  
6 would like us to base everything on the Hamilton read.  
7 So are we, therefore -- is it Tables 38 and 39 that  
8 you would like us to have as the take home message?  
9 That's on pages 64 and 65 of the briefing document.  
10 I just want to make sure that the final take home  
11 message you want us to have is those tables and not  
12 some other tables.

13 DR. DEAN: Okay. Let me ask my medical  
14 team here to respond to you on that as soon as they  
15 can confirm that.

16 CHAIRPERSON RAMSEY: While everyone is  
17 thumbing through, the next to follow, Dr. Patricia  
18 Love will introduce the FDA speakers. So, Patricia,  
19 you could be prepared for that.

20 MR. MADOO: Dr. Links, could you reiterate  
21 the page numbers? For Committee clarification,  
22 apparently Dr. Links is referring to the sponsor  
23 briefing document, the blue binder.

24 DR. LINKS: Right. Pages 64 and 65,  
25 Tables 38 and 39.

1 DR. NICODEMUS: Yeah, I would comment that  
2 it is actually our position that we do believe that  
3 the Hamilton is an appropriate gold standard, and  
4 those tables do appear to be appropriate tables.

5 We also would point out that the results  
6 of Hamilton are consistent with the institutional site  
7 read as a secondary and supportive analysis, and that  
8 I wouldn't want you to discard the information  
9 relative to the institutional site read, which I  
10 believe is very consistent with the results of the  
11 Hamilton results as well, as a secondary endpoint.

12 CHAIRPERSON RAMSEY: We have another  
13 comment.

14 Please state your name first.

15 DR. D'AGOSTINO: Ralph D'Agostino.

16 If we do that, then we're saying that we  
17 don't buy the original protocol primary endpoint  
18 because it was not the Hamilton.

19 MR. MADOO: Do you have a comment, Dr.  
20 Hammes?

21 DR. HAMMES: Yeah, just one comment to  
22 that, which is that the primary endpoint is the same.  
23 The point that we did make was that the true standard,  
24 which I think in a trial of this nature the issue is  
25 what is clinical truth, and we clearly have identified

1 that clinical truth was being inaccurately diagnosed  
2 using the prospective methodology. That, I think, has  
3 been discussed in detail, and so I just would point to  
4 that distinction, which we have reviewed.

5 CHAIRPERSON RAMSEY: Thank you.

6 I'd like to thank the Committee and the  
7 presenters for that session and now turn the podium  
8 over to Dr. Patricia Love, who will introduce the FDA  
9 panelists.

10 DR. LOVE: Hello. Just a couple of brief  
11 comments before the review team presents their  
12 information.

13 First, I'd like to note that we've been  
14 joined at the table by Dr. Lilia Talarico. She's the  
15 Division Director of Gastrointestinal and Hematologic  
16 Products, where some of the therapeutic antiplatelet  
17 products that were mentioned earlier have been  
18 reviewed in the FDA.

19 Also, as often is the case when we're  
20 coming to the end of an action, there is quite a  
21 dynamic that goes on between the sponsors and the FDA.  
22 We've worked a great deal to try to make sure that the  
23 database that's presented to the Committee today is  
24 consistent.

25 However, as we listened this morning,

1 there were a couple of things that we noted that might  
2 be a little bit different from what's in the  
3 application. We've talked to the sponsors about this  
4 during the break, and they have agreed to submit the  
5 additional information, but for your reference two  
6 items might be of interest as you go through your  
7 proceedings today.

8 One is the amount of vitronectin binding.  
9 There's a difference as you'll see from our presenters  
10 and the sponsor, a difference of either 100 or 1,000  
11 nanomolars. That might be a typographical error that  
12 can be resolved.

13 Also, the Hamilton read information  
14 prospective criteria is not in the existing  
15 submission, and the sponsor has agreed to amend that.

16 If someone could just turn on the slide  
17 projector, the overhead there, please.

18 The only other point to make at this  
19 moment is that the review team order of presentation  
20 is going to be different from what is in your agenda.  
21 Dr. Laniyonu will present first, followed by Dr.  
22 Zolman, Dr. Jones, and Dr. Sobhan.

23 Thank you.

24 CHAIRPERSON RAMSEY: Dr. Laniyonu.

25 DR. LANIYONU: Thank you very much, Dr.

1 Love.

2 Good morning. Today I'll be presenting  
3 the review team's pharmacology, toxicology,  
4 perspective of this submission, but before I go into  
5 the details of my talk, I would like to thank Diatide  
6 for the excellence of their submission. There was  
7 many volumes that are well indexed, and it really  
8 facilitated our review process. Thank you very much.

9 As I indicated, I was the review  
10 pharmacologist on NDA 20-887, AcuTect. In doing our  
11 review process, we considered some key review issues  
12 that were unique to this product and some that we  
13 encounter on a day-to-day basis in the division.

14 And these were the key questions that we  
15 asked ourselves. For receptor based agent, we wanted  
16 to know the pharmacological basis of action of these  
17 products.

18 Secondly, we wanted to see whether Diatide  
19 provided us with proof of concept and evaluates those  
20 concepts from a set of criteria that must be fulfilled  
21 by imaging that this interaction with receptor based  
22 kind of them (phonetic).

23 Thirdly, we evaluated the experimental  
24 evidence as presented by Diatide.

25 And finally, we considered the

1 pharmacology for and toxicology issues that arose from  
2 our review process.

3 As submitted by Diatide, the  
4 pharmacological base of action of AcuTect includes the  
5 following, and this is really from the literature.

6 One, that fibrinogen binds to the  
7 glycoprotein 2B3, which subsequently I'll be referring  
8 to as alpha-2, the third receptor, by the sequence  
9 argininyglycyl-aspartic acid, and this can also be  
10 called the RGD sequence.

11 Secondly, that if you synthesize peptides  
12 containing the RGD sequence, that they're capable of  
13 binding to the receptor sites.

14 And finally, radiolabeled peptide. With  
15 continuing this sequence, it should be able to detect  
16 actual platelets in acute deep venous thrombosis.

17 Without going into the detailed mechanisms  
18 of signaling by fibrinogen and other integral  
19 receptors, I would like to say that we actually agree  
20 with Diatide on these three bases.

21 But what are the clinical implications of  
22 an agent that acts via activation of -- that can only  
23 detect difference to both the true activation of  
24 platelets?

25 These are the clinical implications. Just

1 to go over my first point again, implicit to the  
2 proposed mechanism of action is the requirement for  
3 platelet activation. So theoretically AcuTect will  
4 bind with the platelets irrespective of the  
5 pathophysiological process of both the regions  
6 involved.

7 That leads to the difficulty in  
8 distinguishing acute propagating thrombi from  
9 inflammatory actions requiring platelet activation.

10 And finally, you may have the discussion  
11 with pressure activity (phonetic) and background  
12 uptake processes.

13 For the proof of concept evaluation, we  
14 wanted to know how does the affinity of apcitide for  
15 alpha 2, beta 3 receptors of platelet compare with the  
16 affinity of fibrinogen for the same receptor.

17 Thank you.

18 Secondly, we wanted to see how selective  
19 is apcitide for this receptor compared with the  
20 selectivity for the integral receptors sharing the  
21 common beta 3 subunit, for example, the alpha file  
22 (phonetic), beta 3 integral receptors of vitronectin,  
23 which is present on endothelial cell surfaces.

24 For the proof of concept studies, Diatide  
25 submitted the following information. They gave us

1 studies regarding the receptor binding properties of  
2 AcuTect, the binding of apcitide to human platelets,  
3 functional studies, and injury model of venous  
4 thrombosis.

5 This is an in vitro receptor assay in  
6 which we compare the in vitro concentrations, 50 IC-50  
7 for fibrinogen receptor with that for vitronectin  
8 receptor, and as pointed out by Dr. Love, the figure  
9 indicated that this is 1,000 nanomolar. For the  
10 solution that I reviewed, it was stated to be 100  
11 nanomolar.

12 So you have a suggestion in which apcitide  
13 preferentially binds to fibrinogen receptors and less  
14 avidly with vitronectin receptors, suggesting of low  
15 cross-reactivity. Whether this 100 or 1,000, I do  
16 agree with this study that there is little cross-  
17 reactivity with vitronectin receptor sites.

18 Furthermore, they also show that  
19 Technetium labeled apcitide binds specifically to  
20 washed platelets, and that can actually displace about  
21 77 percent of this binding by the process called  
22 bibapcitide, and that when you use a global stimulant,  
23 such as adisen (phonetic) diphosphate to stimulate or  
24 activate platelets, you have a threefold increase in  
25 binding.

1           So these studies demonstrated that you can  
2 actually have in vitro binding to platelets. So you  
3 have two key concepts here. The first is that Diatide  
4 has shown that AcuTect can bind to in vitro alpha 2,  
5 beta 3 receptors, and secondly, you can actually  
6 demonstrate the in vitro binding to activated  
7 platelets by AcuTect.

8           So we need to ask: what are the  
9 consequences or the functional consequences of this  
10 receptor of this AcuTect-platelet interaction?

11           And the first one that you can actually  
12 deduce from the proposed mechanism of action is that  
13 an agent such as AcuTect will actually inhibit in  
14 vitro platelet aggregations, and this are the peptides  
15 that are contained within the formulation when you  
16 give it, and all of them actually inhibits platelet  
17 aggregation, albeit by a different potency.

18           You have the bibapcitide which actually  
19 contains two dimers of apcitide, BB (phonetic), B  
20 equal potent with P1007, which are two dimers, and the  
21 less potent is P1008, which has an individual  
22 concentration of about 700 nanomolars.

23           Furthermore, in ex vivo platelets  
24 aggregation studies, in this case dogs were  
25 administered doses of AcuTect that correspond to

1 either the maximum human dose, which is two microgram  
2 per kg or multiples of this 30x or 100x, and the  
3 percentage platelet inhibition was studied.

4 At the dose equivalent to the dose that a  
5 50 kilogram person would obtain, there was no  
6 inhibition of platelets aggregation. As you increase  
7 the concentration, 30-folds to 100-folds, you have the  
8 30 percent inhibition of platelet aggregation to 90  
9 percent inhibition of platelet aggregation, suggesting  
10 that the dynamic activated platelet better interaction  
11 resulted in a measurable physiological response.

12 In this very vital study, bleeding time  
13 was not systematically studied, and what is critically  
14 missing from this piece of information is that I do  
15 not have the dose or the concentration of AcuTect  
16 between 1X and 30X, at which there was no inhibition  
17 of platelets aggregation. So I really do not know the  
18 safety margin between 1X and 30X for this study.

19 I believe one of the panel members  
20 suggested that some of these studies can actually be  
21 accomplished through in vitro animal studies, and this  
22 is an example of such a study that might easily be  
23 accomplished.

24 Diatide presented data showing that  
25 neither heparin or aspirin affected the anti-

1 aggregatory effect of apcitide. What was missing was  
2 that there was no data to show whether heparin or  
3 aspirin will affect the binding of apcitide with the  
4 receptor.

5 This is important because one of the NDA  
6 submissions, Diatide advanced the concept that maybe  
7 the concentration required for inhibition of platelet  
8 aggregation is far above that would normally be seen  
9 in the clinical setting.

10 While I agree with that, the functional  
11 interaction with receptor is actually critical and  
12 important simply because the concentration that will  
13 inhibit those receptors is invariably the same  
14 concentration range that would be used in clinical  
15 practice.

16 For the efficacy study, data used an  
17 injury model of thrombosis, and as Dr. Lister has  
18 pointed out, it's actually extremely difficult to get  
19 a chronic model. You can actually get a good, acute  
20 model of venous thrombosis.

21 Using the canine venous thrombosis model,  
22 we use a background entwined still embolization coil  
23 in the femoral vein. It was established that the  
24 negative control, Technetium labeled glucoheptonate,  
25 did not image thrombus, and that Technetium labeled

1 P280 or apcitide provided good in vivo visualization  
2 of thrombi, and I'm actually using the words as used  
3 by Diatide.

4 Finally, for the positive control, they  
5 used Technetium labeled HMU PAO (phonetic) platelets,  
6 and they felt that it gave excellent images of  
7 thrombi.

8 They went on to say that a clear advantage  
9 of Technetium labeled P280 compared with the platelets  
10 is that there is rapid excretion. There is rapid  
11 clearance of Technetium labeled in the body compared  
12 with platelet labeled cells, and you have a better  
13 thrombus-to-background ratio.

14 This is a table adapted from Diatide's  
15 submission, and it shows that for the glucoheptonate  
16 you have a thrombus-to-blood ratio of about two, and  
17 for the Technetium labeled P280, you have a thrombus-  
18 to-blood ratio of about four, and for a Technetium  
19 labeled platelets it was about 5.4, again confirming  
20 Diatide's conclusion. Platelets labeled Technetium  
21 seems to give better visualization of these thrombi.

22 The studies, therefore, demonstrated that  
23 you can actually demonstrate binding of apcitide to  
24 the growing thrombus.

25 So all of these studies submitted by

1 Diatide demonstrated that apcitide preferentially  
2 binds to fibrinogen receptors.

3 Secondly, you have in vitro binding to  
4 platelets, and as a consequence of these two effects,  
5 there's a dose related inhibition of platelets  
6 aggregations, and that in an animal model of  
7 thrombosis reflected uptake in thrombi.

8 I still have some lingering questions  
9 though, and the first one is that as submitted by  
10 Diatide, I do not have a clear indication of what's  
11 the NOEL for inhibition of platelet aggregation within  
12 the clinical setting, and the NOEL is defined as the  
13 no observable effects level, that is, the dose of  
14 apcitide that will not affect platelets aggregation in  
15 the clinical setting was absent.

16 And finally, what is the relationship of  
17 the receptor binding of that of alpha 2, beta 3 -- to  
18 the proposed clinical use, and on that note I call on  
19 Dr. Zolman to continue with the presentation.

20 DR. ZOLMAN: Good morning, ladies and  
21 gentlemen. I will present the safety evaluation  
22 perspective on this drug.

23 My name is Joseph Zolman. I am a medical  
24 officer in the Division of Medical Imaging.

25 I reviewed the safety aspects of this drug

1 and concluded that the effect, the untoward effects of  
2 this drug are rather mild. This was judged by the  
3 evaluation of adverse drug events, their nature and  
4 frequency, as well as the effect of the drugs on vital  
5 signs and laboratory measurements.

6 Thus we are in general agreement with the  
7 sponsor that the drugs are relatively safe. However,  
8 this agreement is preliminary based on the nature of  
9 the safety database.

10 As you can see from this overhead, the  
11 total of patients and normals enrolled is 714, and  
12 exposed 710. This is in agreement with the sponsor.

13 Seventy-eight of these patients and  
14 normals were exposed to early formulation and 632 to  
15 proposed for market formulation.

16 Adverse drug events were examined at 632  
17 patients, vital signs at 450 patients, and labs were  
18 measured in 140 patients and normals.

19 However, the question and concern is not  
20 in the total numbers of patients and normals involved,  
21 but with the depth of the observations.

22 As we can see from here, on 169 patients  
23 and normals were followed for adverse drug events for  
24 24 hours. Only 102 patients were followed for vital  
25 signs for 24 hours, and labs were measured for 140

1 patients and normals at three and 24 hours.

2 Therefore, the investigation doesn't  
3 provide sufficient amount of information, and the  
4 safety database is limited because of lack, of  
5 insufficiency of information beyond three hours.

6 As we can see from here, 169 patients were  
7 followed for 24 hours for adverse drug events. This  
8 is a very small number, 632 patients for the total of  
9 three hours. There were no deaths. There was one  
10 serious documented hypotension, and there were 34  
11 adverse drug events in the category of mild and  
12 moderate events.

13 The serious event related to a 34 year old  
14 male five days after motorcycle accident. Following  
15 the administration of the drug, the patient went from  
16 145 systolic pressure to 110 in 15 minutes, and then  
17 later to 70 in 60 minutes.

18 He was treated with fluid infusions and  
19 recovered quickly.

20 The nature and number of mild and moderate  
21 drug events is depicted here. Essentially those were  
22 few in frequency and mild in nature. The numbers  
23 reflect only those who were present more than one hour  
24 during the study.

25 Of these presentation of the various

1 documents may reflect some degree of hypersensitivity.  
2 Even the serious case could be a potential case of  
3 hypersensitivity. However, we don't have the data to  
4 document this accurately and cannot assert it with any  
5 firmness.

6 The mild and moderate drug events could be  
7 related to preexisting conditions, for example, pain.

8 Another safety concern is potential  
9 immunogenicity of the product. The sponsor measured  
10 IgG against the P246 and P1007. P246 is the peptide,  
11 and P1007 is the fragment. This was tested by ELISA  
12 assay in samples taken at a baseline and 21 days after  
13 single dose of AcuTect.

14 The sponsor reported no significant change  
15 in the measures. All results were within two standard  
16 deviations of mean of optical density for preinjection  
17 data.

18 This we consider a parameter information  
19 because this is only one of potential parameters of  
20 immunoresponse which could be measured, and more  
21 definite data is needed, particular in reference to  
22 the parameters which could assess hypersensitivity.

23 As a summary, the review team agrees with  
24 the sponsor in respect to safety data reporting. We  
25 are in agreement with the sponsor that the drug is

1 relatively safe, but with this status this agreement  
2 is preliminary because only a limited number of  
3 patients was monitored beyond three hours.

4 There is lack of information on the labs  
5 so that they have more than three hours to change,  
6 such as creatinine and liver enzymes. There is lack  
7 of data to assess potential hypersensitivity and lack  
8 of data pertaining to repeated dosing issues.

9 There is also lack of information on  
10 bleeding time, which may relate to platelet  
11 aggregation in PT data.

12 Thank you for your attention. This is all  
13 for the safety aspects of this drug. Dr. Jones will  
14 now continue with the efficacy evaluation.

15 DR. JONES: Thank you, Dr. Zolman.

16 Having surmounted that little problem of  
17 technology we're ready to begin.

18 (Laughter.)

19 CHAIRPERSON RAMSEY: The hardest part of  
20 the day is putting that microphone clip on.

21 DR. JONES: Yes, and not piercing your  
22 finger with the pointer.

23 (Laughter.)

24 DR. JONES: It adds to the excitement, I  
25 think.

1 I'd like to start with basically  
2 introducing some of the issues that I want to talk  
3 about this morning. I hope to be very brief since so  
4 much has already been said by the sponsor, and I don't  
5 want to be too repetitious.

6 However, I do want to repeat the claim for  
7 AcuTect, and I do want to address some of the  
8 technical features of the image because they are very  
9 important to the agency to be able to support the  
10 claim for the drug. It's important for us to have  
11 that kind of information to validate the data that  
12 must go into the package insert.

13 The blinded read criteria, I would like to  
14 remind the Committee what has already been presented  
15 by the sponsor. I'll be quite brief about that.

16 I also wish to talk about the case report  
17 forms that the sponsor provided to the blind readers.  
18 There were two report forms that were to be filled  
19 out.

20 The data that was collected then would be  
21 in my Point 4 of the relationship of the image  
22 findings to the proposed use and the issues that seem  
23 to arise from some of those results.

24 The claim for AcuTect, as we all know by  
25 now quite well, is that it is indicated for the

1 scintigraphic imaging of acute venous thrombosis,  
2 emphasis on the word "acute," and that it's venous  
3 thrombosis. There's no mention of phlebitis in that  
4 indication. It's a very distinctive, targeted claim.

5           The technical features of the image. The  
6 technical features are very important to be  
7 established in Phase II since they are the hypotheses  
8 that are to be tested in Phase III to help us with the  
9 labeling, to truly help us establish the truth of what  
10 is being seen by the readers. They're very important.  
11 They should actually be descriptive of a manifestation  
12 of disease.

13           And having met those requirements, they  
14 should be able to be easily incorporated into the  
15 package insert in support of the claim of the sponsor.

16           Reminding everyone again, ad nauseam  
17 perhaps, about the blinded read criteria, the sponsor  
18 required that there be unilateral asymmetry; that the  
19 asymmetry might be in the iliac, thigh, popliteal, or  
20 calf area; that the abnormality be seen on both  
21 anterior and posterior projections; and that the  
22 readers were allowed to adjust the contrast such that,  
23 as noted in Point 4 here, if asymmetry appears only  
24 after extreme contrast enhancement. Then the image  
25 was to be called positive if there's also a diffuse

1 asymmetry. It was to be called negative if there was  
2 no diffuse asymmetry.

3 Now, the case report forms that were  
4 provided to the readers are as follows. I have to  
5 apologize for this one. It does not -- it did not  
6 translate well electronically, but essentially what it  
7 allows the blinded reader to do is to record the site  
8 of positivity and whether or not the positivity is  
9 actually not seen or whether it's inconclusive or  
10 whether it's strongly positive.

11 Having made the determination that there's  
12 actually a positive finding, the reader then went to  
13 the next case report form, which again didn't  
14 reproduce well for me, and I apologize.

15 In this case report form, for all the  
16 positive readings the blinded reader was to note the  
17 side of the abnormality, whether it was iliac in  
18 location, the thigh, the knee, or the calf. The  
19 intensity of uptake was to be recorded, whether it was  
20 slight, moderate, or highly intense. The shape of the  
21 lesions, circular, linear, or irregular, was also to  
22 be recorded, and the extent of vascular involvement  
23 was the final feature.

24 That then took into account all of the  
25 positive readings, positive images, that is.

1           Now, this left us with some limitation of  
2 data. The case report form did not collect features  
3 of negative or indeterminate interpretations. We  
4 actually were not able to get true positive, true  
5 negative, false positive, false negative assessments.  
6 This would have been very helpful to our  
7 statisticians.

8           The sponsor reported the image findings  
9 for the cases believed to be representative of acute  
10 thrombosis. The image findings for the negative cases  
11 were not reported. It's unusual that all cases are  
12 clearly positive in medical imaging studies. What we  
13 don't have is what's the break point between the  
14 negative and the positive image and what's the  
15 variation. What are the imaging endpoints that occur  
16 in that region of interpretation?

17           Similarly, we don't have any data on  
18 patients with phlebitis alone. What did the images  
19 appear like with phlebitis? Perhaps there is no  
20 reason for concern with that since the sponsor  
21 indicates that there is likely to be no localization  
22 of activated platelets in the presence of phlebitis,  
23 at least with AcuTect.

24           So this leaves the review team with some  
25 questions. What are the relationships of the image

1 findings to the proposed use?

2 And as I've said, the question of  
3 phlebitis versus thrombophlebitis to us remains still  
4 a murky area.

5 And the question of distinguishing acute  
6 from chronic thrombosis is also not clear.

7 The issue of anticoagulant therapy and its  
8 influence on image has been discussed a bit already  
9 this morning, and I reintroduce our concern about  
10 that.

11 Repeat doses provide another concern.  
12 This is a diagnostic product. Many imaging products  
13 are used to assess baseline criteria of a disease, and  
14 following therapy they may be repeated again. There  
15 is the possibility that this product could be very  
16 useful in following therapy and may be needed to be  
17 repeated more than one. I'm hypothesizing.

18 That being the case, we've heard earlier  
19 from Dr. Laniyonu that in the preclinical studies,  
20 AcuTect tends to inhibit the aggregation of platelets.  
21 We also wonder about the immunogenicity, as Dr. Zolman  
22 raised the issue. If there's immunogenicity, is there  
23 some possibility that this test they have created  
24 antibodies that may render it less useful or perhaps  
25 even some hazard introduced because of the induction

1 of antibodies.

2           Regarding the collection of safety data,  
3 we realize that 90 percent of the product is  
4 eliminated within the first 24 hours through the  
5 kidneys, and this may have caused the sponsor to have  
6 unnecessarily perhaps shortened the collection time of  
7 safety data.

8           However, the safety data is very important  
9 to us, to be carrying it out particularly if any  
10 abnormal safety data occurs. We want to be able to  
11 follow it until it returns to normal.

12           And the issue that has been the large one  
13 today about the adequacy of the standard, I'm not  
14 going to say very much more about that, except that it  
15 has occurred to us that while venous contrast  
16 phlebography has been accepted by ourselves and the  
17 sponsor as a standard of truth, it really isn't  
18 actually a standard. It's a comparator. If we could  
19 have a standard as someone mentioned, to actually get  
20 the clot and look at the histology, that would be  
21 ideal. It is impossible.

22           We have a unique agent here under  
23 discussion today that's a receptor, and receptor  
24 agents are going to introduce this problem in the  
25 future should any more come along, and I'm sure they

1 will.

2 So this is a big problem, and we need the  
3 Committee's help with this particular issue of the  
4 standard.

5 Thank you very much.

6 DR. SOBHAN: That's the last time you have  
7 to wait for that kind of a struggle with the  
8 microphone.

9 What I'm going to do this morning -- my  
10 name is Mahboob Sobhan. I am the division  
11 statistician on AcuTect.

12 What I'm going to do is revisit some of  
13 the features of efficacy. I understand there are a  
14 lot of questions came out from the panel members as to  
15 the consistency of the result, the comparator used,  
16 and some of the endpoints like sensitivity and  
17 specificity.

18 I'm going to skip some of the study  
19 features because the sponsor has done a good job of  
20 walk you through those things. So I'm going to skip  
21 some of the study features. I'll come to the  
22 endpoint, some of the measured predictions. I will  
23 also skip because Dr. Jones already explained some of  
24 those features.

25 My most focus should be on the results

1 from pivotal studies and then what role CVs play in  
2 this application, and then I'll finish with my  
3 conclusion, summary and conclusion.

4 This is just to revisit. The comparator  
5 is contrast venography or standard of truth, what we  
6 are studying this morning. External of the standard  
7 of truth is no available, which is not possible  
8 probably for venous thrombosis. The objective is to  
9 detect and characterize acute VT compared to contrast  
10 venography.

11 This is an idea you have seen this  
12 morning. Procedure is measuring before and after. I  
13 think it's a matter of convenience rather than order,  
14 randomized order, and images are taken and three  
15 different time points.

16 To show efficacy, this is the -- as far as  
17 protocol, this is the endpoints, the agreement rate,  
18 which is number of positives and negatives detected by  
19 both modalities and sensitivity and specificity, which  
20 I put in the quote. Quote means I call it pseudo  
21 sensitivity. In other words, we don't have the real  
22 truth, 22 carat gold. So I put it in the quote.

23 This is a little bit just to revisit some  
24 of the mathematical or definitions of sensitivity,  
25 specificity in the real situation. If you had a gold

1 truth and you have a test agent that correlates with  
2 the gold, then you can define since you expect like  
3 this, and accuracy which is, you know, defined as  
4 this, and agreement rate used in this application is  
5 a surrogate for accuracy.

6 This will be the scenario for real  
7 situation if you have the gold standard -- I mean the  
8 real standard of truth. As you can see, the sense and  
9 expect (phonetic) is really -- the pivotalness  
10 (phonetic) is also the function of sense and expect,  
11 but we're not going to touch all those issues.

12 The hypothesis as per protocol. I want to  
13 remind you this is as per protocol. The hypothesis  
14 was to reject that the agreement rate of 60 percent is  
15 below -- I mean it's below 60 percent as opposed to  
16 more than 60 percent, and they used this approach to  
17 demonstrate that the product works.

18 I have not seen anything about 75 percent  
19 in the application as such.

20 I'm going to revisit this that was done.  
21 Three things were done. One is I didn't put it in  
22 here, which is the blinded criteria they used to train  
23 the readers, and then this is how the score was done  
24 on the image. This was done even if the patients are  
25 positive, which Dr. Jones showed you through the

1 schematic diagram.

2           Let's focus on the blinded read. There  
3 are three types: blinded read, per protocol, majority  
4 rule decision. For CV three readers, and majority was  
5 the decision. For unblinded read at the institution,  
6 unblinded meaning he or she had access to personal  
7 information, and this is done post hoc consensus. The  
8 AcuTect reads are done by three different readers, as  
9 they pointed out this point. They're made at any time  
10 point and collected by all time points.

11           Let's look at this. This is from the  
12 sponsor's submission. First row is blinded read,  
13 which is originally planned for protocol. You can see  
14 you have seen this number is 45 versus 82, which is  
15 like twofold difference between Study A and B, and by  
16 unblinded it's more consistent to what decided in the  
17 application that the prevalence of venous thrombosis  
18 is 30 to 40 percent. It still is a little bit higher  
19 in Study B, but after these two are done, the analyses  
20 are done, all the facts are known, this is what is  
21 retrospectively done, retrospective meaning after the  
22 facts. After all the studies are completed, this is  
23 the analysis that they have done at Hamilton, and look  
24 at these numbers, 21 versus 33. Again, I agree 33  
25 percent is very close to what the reference or the

1 literature suggested, but here we have a problem also.  
2 It's below, much below what we've seen by the other  
3 two methods on the first row and second row.

4 So the question is: where to reject this,  
5 why do we have to accept this, not mentioning other  
6 problems with the retrospective analysis? Because we  
7 see here almost 20 percent less than in Study A. In  
8 other words, Study B is going in the other direction  
9 than the Study B on Row 1.

10 But for AcuTect readers it's pretty much  
11 consistent, although it's still a little low side.  
12 The range here is for three readers. I am presenting  
13 read one, read two, read three results, 48 to 54  
14 percent, meaning read one, read two, read three  
15 results.

16 And let's focus on read one. That's the  
17 one, two, three. The two was done on all time points,  
18 so let's focus on read one.

19 This is the result they have submitted.  
20 You recall confidence interval of the statistical  
21 approach. This is lower bound and upper bound. The  
22 solid bullet is the point estimate, in other words,  
23 the agreement rate. Let's focus on reader one to  
24 three.

25 If you look at the upper panel, reader

1 one, reader two results, significant. Reader two is  
2 not significant because the lower bound contains the  
3 point estimate, and if you go to the lower panel,  
4 which is Study B, none of them made it. All the null  
5 hypothesis could not be exerted in any of the leader  
6 evaluation (phonetic).

7 In fact, the ideal situation is if we have  
8 all the confidence intervals lying to the right of  
9 this point, the red line, here you have some negative  
10 results. So that's where the decision was made to do  
11 Hamilton read.

12 Let me remind you and let me show you the  
13 unblinded read result. On the unblind result, which  
14 is the reader has access to all patient information,  
15 there is virtually no change in the Study A. All  
16 readers are making, and then two readers are making as  
17 we have seen in the blind read. Here is some  
18 improvement. Only according to one read, which is  
19 read four, it is significant. None of the other five  
20 was significant. So still we're seeing some point  
21 estimate falling beyond 60 percent, but nonetheless,  
22 there is statistical not significant.

23 Let's look at the Hamilton read. Here we  
24 have some inconsistency as far as Study A is  
25 concerned. You are seeing a little bit off here as

1       opposed to blind and unblind read in Study A, but  
2       Study B, almost all made except one. Five out of six  
3       are making it. So we can see the results of Hamilton  
4       makes in B, but it's not consistent with what we have  
5       seen as the protocol in both analyses, blind or  
6       unblind.

7                   What are the implications? Let's look at  
8       some of the agreements. What are the agreements  
9       between AcuTect read one versus blind? Blind, I'm  
10      referring at the same time blind means general read.  
11      You can see in Study A the comparator statistics,  
12      which simply measures the agreement observed minus the  
13      chance agreement. Chance agreement means the mismatch  
14      probability.

15                   So if you look at this, it's still less  
16      than .5, which is not good, as pointed out by the  
17      sponsor also, and in Study B you can see the magnitude  
18      is almost less than half. The AcuTect blinded versus  
19      unblind, it's still poor.

20                   I didn't have the Hamilton read scores.  
21      So I couldn't calculate it, but as you can see here,  
22      both Study A and B, the agreement was really poor  
23      within both methods.

24                   I heard a lot about the sensitivity and  
25      the specificity of CV as well as ultrasound this

1 morning. It was around 90 percent, reported as 90  
2 percent, and here is the sens. and spec. calculated.  
3 Even though we didn't have the real truth, the  
4 estimate, what I call sample sensitivity or pseudo  
5 sensitivity, here you can see AcuTect read one versus  
6 original read. The range is for three readers. It  
7 goes from 60 to 76 in Study A. In Study A it's almost  
8 half, but blind read is better, but here it's much  
9 lower. So I don't see how it is closer to the other  
10 two methods, in other words, CV or ultrasound.

11 So this has some implications for the use  
12 of this product or even the labeling of the product.  
13 How is going to determine or say how this product  
14 works? What is the sensitivity of this? Is it good,  
15 as good as what we have in the market or is it better  
16 or is it less effective?

17 So what I'm showing here is the  
18 sensitivity. Ideally what we like to see is the high  
19 sens. and high spec., but in Study B you see the  
20 specificity is much higher because of what we have  
21 seen in the original contrast with the result.

22 So the message here is the sens. and the  
23 spec. calculated based on the reference standard is  
24 below what we expect. For a modality to be used in  
25 practice, I think the practitioners would like to see

1 as high as possible.

2 Now, the question came to us: which one  
3 are we to use? We have discussed this. The panel  
4 members discussed this morning. This is what's done  
5 in the application. These are the desirable features.

6 Prospectively planned, yes. Unblind, yes.  
7 Prospectively I forgot to mark it. Independence, yes.  
8 Yes. Hamilton, no, because both studies were  
9 interpreted by the same readers. Blinded to patient  
10 history in AcuTect scans, yes. Unblinded, they said  
11 yes. I'm not sure. This is Hamilton read, blinded.  
12 Consistency in this area, I left it unblind because  
13 the image criteria they used by the AcuTect readers  
14 and Hamilton readers were probably different. We have  
15 not seen it, so I can't comment on that.

16 The problems, although there is consensus  
17 read, consensus read meaning you resolve the case, you  
18 know, whether it is positive, negative or whatever.  
19 The study results is dependent upon CV. In B what we  
20 have seen, the inconsistency. That's what I'm  
21 referring to.

22 So ideally the features or the advantage  
23 point is still as per protocol analysis rather than  
24 both unblind or Hamilton, even though the unblind read  
25 is the most often practiced.

1 I read the sponsor -- the patient profiles  
2 in both the studies were the same. Venographies  
3 rather acted comparator other than the standard of  
4 truth. As I mentioned earlier, this has some  
5 implication on the sensitivity and the specificity.  
6 If it is a comparator, it's viewed as a comparator,  
7 and sens. and spec. interpretation is rather  
8 difficult.

9 Both the studies, there was agreement to  
10 study with CV comparator. Therefore, it could not be  
11 determined.

12 The diagnosivity of blinded are different  
13 in Study A and B. That's what we have seen. AcuTect  
14 reads with CV in detecting more than 60 percent of  
15 patients according to 50 percent of the blinded  
16 readers; similar results we have seen by both unblind  
17 and Hamilton reader in Study A, but not in Study B.

18 In B, AcuTect does not agree in any  
19 reader's evaluation. In the same study AcuTect do  
20 agree two out of six, one blinded as CV and five out  
21 of six Hamilton read, and I think the sponsor has  
22 shown subgroup effects on agreement rate were not  
23 statistically significant in both the study and B.

24 So my conclusion was AcuTect NDA lacks one  
25 of the requirements that we have in two adequate and

1 well controlled trials. There is substantial evidence  
2 that what we have here is shown in one study, not to  
3 mention other acute versus thrombi question. Study A  
4 could be considered statistically adequate in support  
5 of the purported indication, and Study B is rather  
6 weak or negative. So we don't really support that  
7 that should be considered.

8 That's all. I conclude.

9 CHAIRPERSON RAMSEY: Thank you.

10 And I'd like to thank all of the FDA  
11 speakers for their efficient presentation, and we're  
12 right back on time now, and according to our program  
13 the next would be Committee questions on the FDA's  
14 presentations.

15 So I would like to ask if anyone on the  
16 Committee has any questions at this time.

17 Yes, Dr. Hammes.

18 And if all the questioners and responders  
19 could please state your name first, it makes it a lot  
20 easier for the record keeper.

21 DR. HAMMES: Richard Hammes.

22 A question for Dr. Laniyonu. Trying to  
23 get the biochemistry of this thing a little clearer in  
24 my mind, a decade or so ago I had the opportunity of  
25 doing some platelet aggregation work with a protein

1 that was secreted by platelets called thrombospondin,  
2 and as I recall, that was involved in the initial  
3 platelets sticking together, and it seems to me it  
4 also was involved in interactions with endothelium.

5 Is that the vitronectin receptor that you  
6 were talking about? Are we talking about the same  
7 receptors here with this product? Do you know? Are  
8 you at all familiar with that?

9 CHAIRPERSON RAMSEY: Please use the  
10 microphone.

11 DR. LANIYONU: I'm not sure whether, you  
12 know, the product that you worked with would be  
13 working on vitronectin receptors or not. The  
14 vitronectin receptors are present on the endothelial  
15 cell line, and you do not actually have the  
16 glycoprotein 2B3 receptors on endothelial. They are  
17 increased and situated on the platelets.

18 What this product is showing is a high  
19 degree of selectivity for the alpha 2, beta 3  
20 receptors, and I do believe that the probability of  
21 cross-reactivity with other integrin receptors will  
22 rather be low, but I'm not sure whether I can directly  
23 relate the receptors you studied before to the ones  
24 that have been proposed in this application.

25 DR. HAMMES: Another question. Is there

1 any information on the time course of the availability  
2 of these receptors? Do we know in the process of clot  
3 formation when these receptors are no longer  
4 available?

5 DR. LANIYONU: That's actually key and  
6 critical questions because the platelet's involvement  
7 with thrombi formation or propagation is actually  
8 limited to the initial stages of thrombi formation.  
9 Platelet formation is one of the earlier key steps  
10 required in the process, and so really you are dealing  
11 with a product that would be uniquely sensitive to the  
12 narrow time frame.

13 And the clinical implications of that is  
14 that, at least to my knowledge, that if a patient is  
15 not available at the time period of the development  
16 for this diagnostic imaging, becomes extremely  
17 critical because from my understanding of the concept,  
18 once that window of opportunity is missed, I do not  
19 really see why, if we're just talking about this  
20 proposal, why those patients should be caught.

21 CHAIRPERSON RAMSEY: Yes?

22 DR. ROHDE: Yes. Charles Rohde from Johns  
23 Hopkins.

24 I have a question about the presentation  
25 of Dr. Sobhan. Am I pronouncing your name correctly?

1           The sponsor in the protocol clearly  
2 indicates one sided confidence bounds, and yet your  
3 presentation gives 95 percent confidence intervals,  
4 and they are distinctly different, and I don't want  
5 the Committee to be misled by the fact that your lower  
6 bounds are a lot lower than theirs, as they should be.

7           DR. SOBHAN: No, the protocol say they are  
8 going to construct the confidence interval around the  
9 point estimate, and if the lower bound includes the  
10 point estimate, then they're going to reject the  
11 number.

12           DR. ROHDE: Well, that is not what was  
13 presented; is that correct? We need to get that  
14 clarified.

15           Are there really 95 percent intervals and  
16 you've reported just below the bounds or are they one  
17 sided 95 percent confidence --

18           CHAIRPERSON RAMSEY: Please use the  
19 microphone for a response.

20           DR. ROHDE: It gets back to Professor  
21 D'Agostino's question earlier about what's a one sided  
22 or two sided.

23           CHAIRPERSON RAMSEY: State your name.

24           DR. BALSER: John Balser, consultant to  
25 Diatide.

1 CHAIRPERSON RAMSEY: Thank you.

2 DR. BALSER: They are truly one sided  
3 confidence intervals. They are not two sided, and it  
4 was prospectively stated in the protocol as such.

5 DR. SOBHAN: Okay. That's fine. You are  
6 looking at the lower bound only.

7 DR. ROHDE: No, they --

8 DR. BALSER: No, they're one sided  
9 confidence intervals. We're not just looking at a  
10 lower bound in a two sided confidence --

11 DR. SOBHAN: Yes, but protocol, you wanted  
12 to test -- you specifically stated if the lower bound  
13 includes the point estimate, they're going to reject.

14 DR. BALSER: The one sided lower bound.  
15 That's correct.

16 DR. SOBHAN: Fine, but still what I'm  
17 saying is that's what you intended to show.

18 DR. BALSER: The problem is if you do a  
19 one sided --

20 DR. SOBHAN: You are concerned only with  
21 the lower bound.

22 DR. BALSER: No, we are concerned with a  
23 lower bound of a one sided confidence interval.

24 DR. SOBHAN: Right, but --

25 DR. BALSER: That is not the same as the

1 lower bound of a two sided confidence interval.

2 DR. SOBHAN: Right. Ideally you wanted to  
3 see that you were on the right side of that. Your  
4 confidence interval should be on the right side.

5 DR. BALSER: That's correct.

6 DR. SOBHAN: That's what you specified in  
7 the protocol.

8 DR. BALSER: That's correct, but --

9 DR. SOBHAN: We have talked about the  
10 situation that the protocol states many, many times.

11 DR. BALSER: I'm still not sure I  
12 understand why you're concerned because it's clearly  
13 stated in the protocol it's a one side confidence  
14 bound. It is not a two sided.

15 DR. SOBHAN: I am not disagreeing with the  
16 conclusion, but you are saying -- I'm just showing it  
17 on the slide. That's what you have shown in the  
18 application.

19 DR. BALSER: No, you're showing on the  
20 slide a two sided confidence interval.

21 DR. SOBHAN: That's fine, but --

22 DR. BALSER: The calculation is quite  
23 different.

24 CHAIRPERSON RAMSEY: Dr. D'Agostino has a  
25 comment.

1 DR. D'AGOSTINO: There is a table  
2 presented by the sponsor where they identify  
3 significant results, and the count is still the same  
4 whether it's one sided or two sided.

5 DR. BALSER: That's actually not quite  
6 true, but --

7 DR. D'AGOSTINO: Well --

8 DR. BALSER: I mean, the institutional  
9 read, actually there are two --

10 DR. D'AGOSTINO: Well, I'm talking -- I'm  
11 sorry. I'm looking at the Hamilton read.

12 DR. BALSER: Yes, the Hamilton is fairly  
13 robust to that issue.

14 DR. D'AGOSTINO: Yeah, the Hamilton stays  
15 the same.

16 DR. BALSER: That's correct.

17 DR. D'AGOSTINO: It's an important  
18 question in terms of our interpretation, and this is  
19 what I was trying to get at. I think we should  
20 understand it.

21 DR. WELCH: Yeah, Mike Welch here.

22 I think the two sided confidence interval  
23 would be more enlightened for our statistical policy.  
24 We typically for non-feriority studies look at two  
25 sided intervals, and I think we have, you know, an

1 opportunity to do this and look at the data in that  
2 way, although the one sided was specified in the  
3 protocol.

4 CHAIRPERSON RAMSEY: Yes, Dr. Choyke.

5 DR. CHOYKE: I'd just like to ask someone  
6 from the FDA just to clarify in my own mind the  
7 requirement for two independent blinded studies. I  
8 mean, is that something that's written in stone or is  
9 there wiggle room on that? I mean, what's the wording  
10 of your requirement?

11 DR. LOVE: Okay. That's a major issue.  
12 There is an efficacy standard document that's out for  
13 comment that talks about that particular issue. There  
14 are some specific examples state in there where the  
15 agency might accept one study in certain  
16 circumstances.

17 However, the agency's requirement says  
18 "studies" for the Center for Drugs we're speaking of.  
19 Different centers may also have different  
20 requirements.

21 So one study is generally considered the  
22 exception, but those are stated in that particular  
23 document.

24 CHAIRPERSON RAMSEY: Dr. Links.

25 DR. LINKS: A couple of questions. First,

1 a follow-up to that.

2 It seems to me that we need clarification  
3 on the definition of the word "independent" in terms  
4 of having pivotal studies because clearly this is a  
5 case where the AcuTect reads and the patient  
6 populations were totally independent, and the only  
7 thing that was in any sense dependent was the same  
8 gold truth laboratory.

9 So I'm not convinced there aren't two  
10 independent pivotal trials. I mean, my interpretation  
11 would be that there are, in fact, two independent  
12 trials. Now, whether or not you like the outcomes of  
13 them is a different issue, but to me they're  
14 independent.

15 DR. LOVE: Okay. I think it depends on  
16 how you tease apart the sentence and the words. Okay?  
17 There were two trials prospectively designed that were  
18 independent, and if you look at the original blinded  
19 read, they are independent. If you look at the  
20 Hamilton blinded read, because the same three readers  
21 read Hamilton for both Study A and Study B, that's why  
22 Dr. Sobhan is saying the Hamiltons reads are not  
23 independent.

24 DR. LINKS: May I clarify that?

25 CHAIRPERSON RAMSEY: Please.

1 DR. LINKS: I could certainly understand  
2 if you're going to introduce a new radiopharmaceutical  
3 you want at least two trials so you can be certain  
4 that across a spectrum of nuclear medicine physicians  
5 you'll get comparable diagnostic accuracy in your  
6 interpretations.

7 What I don't understand is the need to  
8 have so-called independence in establishing the gold  
9 standard or the truth for the comparator.

10 DR. WELCH: Yeah, Mike Welch again. I  
11 think there remains confusion on the differences  
12 between a comparator for active control arm and the  
13 gold standard. I think if you're talking about a true  
14 standard of truth, that is, unquestionable, one can  
15 argue that can be used in two individual studies and  
16 the results would be independent.

17 Here we all agree, I think, that the  
18 comparator is error prone, and whatever false positive  
19 or false negative error rates it would have would  
20 certainly influence any biases in estimating  
21 sensitivity and specificity.

22 So judging this as a comparator, I think  
23 we need to be comfortable that the comparator was  
24 judged independently in both studies.

25 DR. LINKS: Got it.

1 May I as one more question?

2 CHAIRPERSON RAMSEY: Certainly.

3 DR. LINKS: I'm still hung up on acute  
4 versus chronic, and the reason I'm hung up on it is  
5 that in the past we've certainly recommended approval  
6 of radiopharmaceuticals that had even less agreement  
7 with a comparator, and we did so because they would  
8 still clinically impact patient care in a very  
9 positive way, and there were no competing imaging  
10 techniques.

11 And from a pharmacologic point of view, I  
12 really want to know what is the actual evidence that  
13 exists, not the theoretical why it should work, but  
14 the actual evidence that this is an agent for acute VT  
15 because it seems to me the only real evidence is that  
16 there's a three times increased binding to activated  
17 platelets, and if I put on my PET brain receptor  
18 imaging hat, a three-to-one specific to nonspecific  
19 ratio -- I'm making a leap here perhaps -- would not  
20 be something to dance in the streets about in terms of  
21 saying this is a very specific agent.

22 And we are talking about receptor imaging  
23 here, and I just don't see it. I mean, am I missing  
24 something?

25 DR. JONES: Well, I'm in agreement with

1 your concern. The ability to distinguish acute versus  
2 chronic, chronic wasn't looked at, and it remains a  
3 question, and certainly for a receptor based agent,  
4 you having that experience could speak to it better  
5 than I, but I had hoped for a better than three-to-one  
6 ratio.

7 So I don't disagree with you.

8 CHAIRPERSON RAMSEY: Are there any other  
9 questions?

10 Dr. Ponto.

11 DR. PONTO: Yes. I have some questions on  
12 the final formulation. It's my understanding that  
13 there are three peptides in the final formulation.  
14 There is the active agent, and there's the P1007 and  
15 the P1008.

16 In the briefing documents it said that  
17 those other two peptides do not label to Technetium or  
18 are not labeled by Technetium. Am I understanding  
19 that there are the three peptides in the final  
20 product? And what evidence is there that Technetium  
21 does not label to any of the others?

22 DR. LOVE: That's somewhat a proprietary  
23 chemistry question. I have to ask first the sponsor  
24 if they want to address it first maybe.

25 MR. PIPER: There is on the agenda a one

1 hour time for a closed session to address issues like  
2 this because they are getting into proprietary  
3 chemistry issues. So we'd prefer to do that.

4 CHAIRPERSON RAMSEY: Please identify  
5 yourself.

6 DR. HAGGERTY: Bob Haggerty, Diatide.

7 From the question posed earlier in  
8 relation to --

9 CHAIRPERSON RAMSEY: Could you please  
10 activate the microphone?

11 DR. HAGGERTY: Bob Haggerty, Diatide.

12 In the question posed earlier for the  
13 regulatory standpoint of two adequate and well  
14 controlled pivotal trials, I did want to just  
15 emphasize that there is a precedent within the agency  
16 of accepting one adequate study for this type of  
17 approval in the past.

18 CHAIRPERSON RAMSEY: Any other questions  
19 or comments from the Committee members?

20 DR. D'AGOSTINO: Could I ask one?

21 CHAIRPERSON RAMSEY: Dr. D'Agostino.

22 DR. D'AGOSTINO: I'd like to ask the FDA  
23 the question that came up this morning in terms of  
24 shifting to the Hamilton. If you perform your study,  
25 you run your analysis, and then you're overwhelmingly

1 hit with the fact that the positive rates are too high  
2 by your blinded readers, and then you move to a new  
3 set of blinded readers, a new procedure for getting  
4 results, such as Hamilton, how do you respond to that?

5 I think that a good part of the sponsor's  
6 argument rests on the fact of shifting to the Hamilton  
7 reading in terms of the efficacy of the studies. Is  
8 there a response? Is it because we found that in A  
9 that the positive rates get so low that it throws a  
10 question into shifting or what's your response to it?

11 DR. SOBHAN: If I understood it clearly,  
12 you are saying that how do we accept Study B or how --

13 DR. D'AGOSTINO: How do you respond to the  
14 move or the concern that the data just on the face  
15 isn't correct with the blinded readers in Study B?  
16 That was found after they did the analysis and so  
17 forth, but nonetheless it was found, and they shifted  
18 to the Hamilton. Now they have a new set of results  
19 which on the surface look good, and if you never saw  
20 the blinded CV readings, you'd be probably impressed  
21 by it.

22 So how do you respond?

23 DR. SOBHAN: We have not seen until the  
24 submission came in what was the -- how they have done  
25 Hamilton or what is the result of Hamilton. As for

1 protocol, what we had is blind and unblinded read.

2 Now, when the submission came in, when we  
3 saw Hamilton read, we knew the fact that it was done  
4 retrospectively. So ideally we would like to still  
5 see our results as per protocol, not the retrospective  
6 analysis after the facts are known.

7 So our position -- I think my position,  
8 and I'm not speaking for everybody else; my position  
9 is in the study design, in the clinical studies you  
10 should not rely on the results after the facts are  
11 known.

12 DR. D'AGOSTINO: Thank you.

13 DR. ROHDE: Yes, Chuck Rohde from Johns  
14 Hopkins.

15 If we pushed that line to its ultimate, if  
16 the sponsor were to run another trial, then it's well  
17 known that there is no way they could ever show that  
18 this product worked because the statistical  
19 significance is .06 now. You run another study. It  
20 can't be reduced. It's .06 plus the probability, et  
21 cetera, et cetera, et cetera.

22 So it seems to me that the real issue is  
23 the scientific issue. Is the Hamilton study the one  
24 to go from the standpoint of it correctly assesses  
25 what's going on with this group of patients? That's

1 the issue, not these little statistical arguments  
2 about this or that.

3 So I think the rest of the Committee, if  
4 they could focus on the scientific aspect, is that a  
5 good study, you know, then we could not worry about  
6 whether they're one sided or two sided or whatever.

7 CHAIRPERSON RAMSEY: Is it four carat or  
8 14 carat, huh? That's really where we're at.

9 Dr. Hammes.

10 DR. HAMMES: Richard Hammes.

11 A comment on Dr. Links' point about  
12 ratios. The parameters I've seen, it's clear to me  
13 that we're talking about much more than a three-to-one  
14 target/nontarget ratio, and I would submit that it's  
15 probably related to the concentration of platelets in  
16 the clot also. So we're dealing with the product of  
17 the two in these concentrations, plus the increased  
18 affinity because those images understandably -- I'm  
19 sure those are the best ones they had, but they are a  
20 much higher ratio.

21 CHAIRPERSON RAMSEY: Dr. D'Agostino.

22 DR. D'AGOSTINO: Just I think the sponsor  
23 does have a way out if we recommend another study  
24 because they don't have to combine the studies. They  
25 could do two positive studies. They could have

1 negative studies mixed in their pool; isn't that  
2 correct? It has to be two positive studies?

3 CHAIRPERSON RAMSEY: Any other questions  
4 or comments from the Committee?

5 We will break for lunch. I'm looking at  
6 my watch, and it's 12:22. We will not have a closed  
7 session this afternoon. We will go directly to the  
8 discussion of the Committee questions for  
9 consideration, and that will begin, and I'd like to  
10 ask -- and, Mr. Madoo, you can make any corrections  
11 here to me if you'd like -- that everybody be back at  
12 1:25. Thus we will begin promptly at 1:30 for this  
13 afternoon's deliberations.

14 Question?

15 DR. PONTO: I did have a question that I  
16 was told they had the answer to.

17 DR. AUGUST: Yes, can we bring that  
18 question on?

19 CHAIRPERSON RAMSEY: Mr. Madoo is asking  
20 if you feel that's absolutely essential.

21 DR. PONTO: I guess not.

22 CHAIRPERSON RAMSEY: Okay. Mr. Madoo?

23 MR. MADOO: Yes. Just by way of noting,  
24 there apparently is a buffet downstairs for 5.95, and  
25 it's called the "soup and salad opera."

1 (Whereupon, at 12:20 p.m., the meeting was  
2 recessed for lunch, to reconvene at 1:25 p.m., the  
3 same day.)  
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(1:26 p.m.)

CHAIRPERSON RAMSEY: I'd like everyone to take their seats if we could, please, and the Committee members to come to the table so we can begin promptly at 1:30.

We plan no moving through this cautiously, but as efficiently as possible. We'll move forward. I don't think it's quite two minutes. I guess we can't really start early, right? It's like closing the plane door before the scheduled time.

But there's a couple of things I want to talk about. We obviously have some important things, including a vote at the end of the meeting, and there's a few things after talking to Dr. Love and others that we would like to clear up.

One, we want to make sure that everybody, the statisticians, in particular, are in agreement or had their questions answered regarding the lower boundary of 60 percent or the other higher boundary for the inclusion or the final conclusion on the study. So we may want to reopen that again if people didn't understand exactly what that was.

And also to the manufacturers and to the panelists why we accept the Hamilton data and analysis

1 after the fact, if you will, if that's the right way  
2 of putting it, when this is not the way we usually  
3 approach a process.

4 In other words, we looked at it. We  
5 didn't like it. We looked at it again, and if that's  
6 okay, then why we're willing to accept that.

7 So I'd like to come back to those issues  
8 later on during the course of the meeting. So you can  
9 be thinking about it, please, while we go forward.

10 And now, Mr. Madoo, we are at the  
11 committee consideration of agency proposed questions,  
12 and these questions are available on the desk if  
13 anybody didn't get a copy of them.

14 And, Dr. Love, you wanted to make a few  
15 statements before we begin or no?

16 I think Mr. Madoo is going to give me the  
17 charge, which is to read this into the record; is that  
18 correct?

19 MR. MADOO: Yes, or if you would like, Dr.  
20 Ramsey, at your discretion you might want to build up  
21 to a particular question by having some more  
22 generalized discussion before we hard copy anything.  
23 As you wish.

24 CHAIRPERSON RAMSEY: Well, I'll leave it  
25 up to the discretion the Committee. These questions

1 that are listed here, one through six, will have to be  
2 read at some point into the record, which I will do.

3 Do we want to go right to those questions  
4 or do we want to have other discussion prior to that?  
5 And are the statisticians here?

6 Perhaps, Dr. Love, maybe you can formulate  
7 the question again so that we can address it to  
8 everybody's satisfaction, if you would be willing to  
9 do that.

10 DR. LOVE: Okay. I suppose one of our  
11 questions asked, after we finished the break I just  
12 wanted personally to be sure that the responses that  
13 Dr. Welch and Sobhan were giving were addressing the  
14 concerns of the panel statisticians. From my hearing  
15 of the conversation, I'm not sure we all walked away  
16 with the same feelings. That's the main question.

17 So I'm just wondering from your  
18 perspective has the question been answered.

19 DR. D'AGOSTINO: Well, Ralph D'Agostino.

20 I think in terms of the lower bound of the  
21 confidence interval that I think it's fine. The  
22 protocol said one sided, and the 60 percent is the  
23 lower limit, I think, is clear, and I don't think it  
24 changes whichever you do.

25 With the Hamilton, it's quite a different

1 discussion, and let me just say what I'm worried about  
2 is that the Hamilton might be the ideal way of viewing  
3 these procedures. The problem is it was not the  
4 protocol specified.

5 And what we have before is, we have the  
6 discussion is the Hamilton right to look at. That's  
7 number one, but then we also have how do we interpret  
8 our data that's before us because it's retrospective  
9 and it came out to be positive.

10 But all the retrospective analyses that  
11 aren't positive never made it here. I mean it's  
12 clearly here, and it clearly looks good. If it didn't  
13 look good, they never would have presented it.

14 So from a statistics point of view, there  
15 really is no way, is what I was trying to get; there  
16 really is no way. It's not a statistical adjustment.  
17 There really is no way that I can see that one can  
18 talk about making a statistical adjustment for the use  
19 of the Hamilton.

20 It's a retrospective analysis. We know we  
21 only see retrospective analysis when they turn out to  
22 be positive. So we have to grapple with the issue of  
23 do we think the Hamilton is the right thing to do and  
24 do we want to ignore the fact that we can't put a  
25 statistics judgment really on this second study, and

1 I think that's the way I would present it to the  
2 Committee in terms of the issues.

3 CHAIRPERSON RAMSEY: Are there any other  
4 comments?

5 DR. ROHDE: Yeah, I would. Chuck Rohde.

6 I would agree with Ralph's comment. You  
7 could look at the analysis of the second set of data  
8 in a slightly different way. You could say what we  
9 really had here are two response variables.

10 We had one response variable comparing to  
11 the completely blind, and then we have another  
12 response variable comparing to the Hamilton data.  
13 Either way there's still an issue of the fact that one  
14 was done after the fact and wasn't in the protocol.

15 And the question is: do the results  
16 constitute good enough science to overcome that? And  
17 that's a matter that I can't judge as a statistician,  
18 but I think the panel ought to satisfy itself that  
19 that science is good enough. Then the decision is  
20 made on that basis.

21 DR. LOVE: I think those certainly were  
22 the concerns from the review team's perspective as  
23 well, and the reason for a lot of discussion today.

24 CHAIRPERSON RAMSEY: Thanks, Dr. Love.

25 Well, you all can be thinking about that,

1 and while you do that then I think, Mr. Madoo, would  
2 it be appropriate at this time to read this into the  
3 record?

4 MR. MADOO: Certainly.

5 CHAIRPERSON RAMSEY: Okay. This, again,  
6 are the questions, and the reason I'm reading them is  
7 just to get them into the permanent record. So you'll  
8 forgive me for that.

9 I'm going to skip the first paragraph and  
10 start here with just number one.

11 Proof of concept relationship to the  
12 proposed indication. Implicit in AcuTect's proposed  
13 use to detect acute venous thrombosis is the need for  
14 to -- oh, for -- thank you -- apcitide bind to  
15 activated platelets and to preferentially distinguish  
16 activated platelets from other cross-reacting binding  
17 sites in the endothelium. Such distinctions affect  
18 AcuTect's potential to affect the differential  
19 diagnosis of acute thrombosis, chronic thrombosis,  
20 phlebitis, and thrombophlebitis.

21 Also, activated platelets are found in  
22 acute thrombosis and in the inflammatory process of  
23 phlebitis.

24 (a) Is there sufficient mechanism of  
25 action information to confirm that apcitide binds

1 preferentially to the alpha 2, beta 3 receptor, and  
2 that it can distinguish activated platelets from  
3 vitronectin receptors in the endothelium?

4 (b) Is there sufficient mechanism of  
5 action information to support the potential to  
6 differentiate acute thrombosis and acute phlebitis?

7 Two, AcuTect image technical features.

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

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

18 Three, standard of truth and efficacy  
19 results.

20 The pivotal Phase III trials are designed  
21 as agreement studies. An external standard of truth,  
22 example given, histopathology, is not available.  
23 Therefore, the assessment of the agreement depends  
24 upon the comparator imaging study and, as such, it is  
25 important for the results to be blinded.

1 (a) Contrast venography results provided  
2 the reference diagnosis. Contrast venography  
3 interpretations are influenced by the reader's  
4 approach or similarity of the criteria used. As such,  
5 the results of the contract venography and the results  
6 of the primary outcome variable are dependent on which  
7 blinded read is used to determine the reference  
8 diagnosis.

9 The prospectively planned blinded read  
10 preserves the independence of the two pivotal trials  
11 (280-32A and 32B). The Hamilton read was  
12 retrospectively performed after the original study  
13 results were known. Also, the Hamilton read is not  
14 independent across both studies. Neither blinded read  
15 of the contrast venograms used prospectively  
16 standardized criteria to interpret the findings.

17 Question: Which blinded read do you  
18 recommend should be used to determine the contrast  
19 venography results, i.e., the prospectively planned  
20 blinded read or the Hamilton retrospective blinded  
21 read or neither?

22 (b) As an agreement study, the target of  
23 a 60 percent lower confidence bound reflects agreement  
24 of AcuTect with either positive or negative contrast  
25 venography results. The trials do not have an

1 external standard of truth. Therefore, a true  
2 sensitivity and specificity assessment is not  
3 possible.

4 Similarly, an assessment of true false  
5 positive and false negatives is not possible.  
6 Consequently, the implied clinical use as a screening  
7 modality, adjunct, alternative, or replacement for  
8 contrast venography is not clear.

9 Question: Is there sufficient information  
10 from the agreement of AcuTect and contrast venography  
11 results to develop labeling recommendations for  
12 clinical use?

13 (c) Given the above considerations,  
14 please respond to the following:

15 Number one, do you recommend accepting  
16 Study 280-32A as one of the two pivotal studies to  
17 demonstrate the efficacy of AcuTect for scintigraphic  
18 imaging to detect acute venous thrombosis?

19 Two, do you recommend accepting Study 280-  
20 32B as one of the two pivotal studies to demonstrate  
21 the efficacy of AcuTect for scintigraphic imaging to  
22 detect acute venous thrombosis?

23 Four, safety. For patients who received  
24 the proposed for market formulation, the database  
25 provides the results of adverse event reporting in at

1 least 632 patients up to three hours and up to 169  
2 patients up to 24 hours. It does not contain data on  
3 creatinine or liver enzymes at the time points when  
4 changes are apt to be detected (if they occur). The  
5 in vitro data suggest that apcitide binding can  
6 inhibit platelet aggregation. The potential clinical  
7 manifestations were not tested with in vivo bleeding  
8 time measurements.

9 Question: Is there sufficient information  
10 to support the safety and reasonable labeling of  
11 AcuTect?

12 Approvability, Part 6. In reference to  
13 the considered information, please address the  
14 following. I think that's actually Part 5, but that's  
15 okay.

16 (a) Do you recommend AcuTect as  
17 approvable for the scintigraphic imaging of acute  
18 venous thrombosis?

19 Question: is there any other indication  
20 that you recommend?

21 Question: If you do not recommend AcuTect  
22 as approvable, are there other studies or trial  
23 designs that you would recommend be completed before  
24 approval?

25 Question: If you recommend AcuTect as

1       approvable, are there other studies for efficacy or  
2       for safety that you would recommend as a Phase IV  
3       commitment?

4               MR. MADOO:  If I may interject now, when  
5       Committee members are voting, the presumption is that  
6       your options are a vote for yes, a vote for no, or an  
7       abstain to any given question.

8               Thank you.

9               CHAIRPERSON RAMSEY:  Dr. Love, could you  
10       please repeat again the meaning of "approvable" as  
11       opposed to "approved"?

12              DR. LOVE:  In general term, approvable is  
13       just before we do a final approval action.  We usually  
14       interpret that to mean there is sufficient information  
15       in the application that we feel that any particular  
16       issue on which you're voting, approvable do not have  
17       to change if we need addition information.

18              The main reading for wording it as such  
19       though is there may also be other outstanding issues  
20       maybe from CMC or other concerns that have to be  
21       sorted out.  So the full direct approval decision may  
22       not be made.

23              CHAIRPERSON RAMSEY:  Can anyone ask a  
24       question?

25              MR. MADOO:  They're free to ask a question

1 as they see fit.

2 CHAIRPERSON RAMSEY: Okay. Panel members,  
3 we are at freedom here. Dr. D'Agostino.

4 DR. D'AGOSTINO: Just for clarification,  
5 are the consultants voting?

6 MR. MADOO: Yes, yes, everyone around the  
7 table, all 12 of you are voting.

8 CHAIRPERSON RAMSEY: Dr. Links.

9 DR. LINKS: Another process oriented  
10 question. Are we going to just go through these  
11 questions one by one and see if we're satisfied? Are  
12 we actually voting on each question or only the  
13 ultimate one dealing with approvability?

14 MR. MADOO: I'll defer that response to  
15 Dr. Love. Do you desire a discrete vote on each  
16 question or do you desire a vote simply on the  
17 approvability question? We could formulate Committee  
18 consensus on the other questions.

19 DR. LOVE: Right. I was going to say  
20 consensus would be okay. Certainly if the Committee  
21 wants to do that, that's fine. It doesn't have to be  
22 a vote as long as we can have enough information to  
23 see how all the different issues are being addressed.  
24 That would be helpful to us.

25 CHAIRPERSON RAMSEY: Dr. Ponto?

1 DR. PONTO: Dr. Love, we have in the past  
2 when we've had applications before us had much more  
3 information with respect to what the labeling is going  
4 to look like than we have on this one. Part of our  
5 approvability decision would be based on what the  
6 labeling is going to be.

7 For instance, the imaging protocol that  
8 they're recommending is not explicitly stated. Things  
9 about the formulation are not explicitly stated.

10 So are we in a situation where we would  
11 recommend that you then use your judgment with respect  
12 to these issues?

13 DR. LOVE: Right, for labeling, yes.

14 CHAIRPERSON RAMSEY: Thank you, Dr. Ponto.  
15 That was a good question.

16 Any other comments or questions from the  
17 Committee?

18 And then I guess I would propose that we  
19 kind of look maybe a 1(a) and 1(b), the little actual  
20 questions and develop a consensus, and then after we  
21 do that move through all of these, and then move to  
22 the final questions. Does that sound reasonable?

23 All right. Let's go then in order since  
24 that's the way they're printed on the paper. One (a),  
25 is there sufficient mechanism of action information to

1 confirm that apcitide binds preferentially to the  
2 A2/B3 receptor and that it can distinguish activated  
3 platelets from vitronectin receptors in the  
4 endothelium?

5 Dr. Links.

6 DR. LINKS: At the risk of going overboard  
7 on this acute versus chronic and acute versus anything  
8 else issue, I would like to pose a question.

9 I like the way the introductory paragraph  
10 under number one states it because it's much broader  
11 than the questions (a) and (b) ask, and it seems to me  
12 that the real question is what would be needed as  
13 evidence to say that this is an acute VT imaging  
14 agent, and presumably the questions under (a) and (b)  
15 would be part of what's needed as evidence, but what  
16 I'm throwing open to everyone is are (a) and (b)  
17 sufficient evidence to label this an acute VT agent.

18 In other words, as an example, there's  
19 certainly no data, clinical data, shown that in  
20 patients who have chronic DVT but no acute VT that the  
21 imaging results are negative. That's an example of  
22 some additional evidence that might further the claim  
23 that this is an acute VT imaging agent.

24 CHAIRPERSON RAMSEY: Dr. Konstam.

25 DR. KONSTAM: But I'm not sure how

1 important that is because if, in fact, you agree that  
2 it's accurate in the setting of detecting acute  
3 thrombus, then the issue is not -- I mean,  
4 interpreting it that way, the issue is not before us,  
5 what happens in chronic.

6 I mean we're going to get into questions  
7 of what are we talking about by acute and chronic, but  
8 I guess they're asking for an indication for acute.  
9 I don't know if Dr. Love wants to comment on this, but  
10 it may not be -- from that perspective, I don't think  
11 it's important whether or not it works in chronic or  
12 how it works in chronic.

13 DR. LINKS: Just a question of  
14 clarification then. My own personal confusion is that  
15 whenever you talk about the specificity of an imaging  
16 agent, you always have to say specificity for what,  
17 and if it's acute VT, meaning it's VT versus no VT,  
18 that's different than it's specific for acute VT.

19 And since the indication is for acute VT,  
20 I just want clarification on what we need as  
21 sufficient evidence.

22 CHAIRPERSON RAMSEY: Would it be  
23 appropriate to ask the manufacturers at this time, Mr.  
24 Madoo, for comments if they'd care to make any?

25 MR. MADOO: If the Committee deems it

1 constructive.

2 CHAIRPERSON RAMSEY: Yes. I see yeses.

3 Would the manufacturers care to make any  
4 comments? Did they understand the question?

5 DR. DEAN: Yes, I think we understand the  
6 question. It's a two-part question here, and I think  
7 one relates to biology and one relates to the clinical  
8 manifestations, but I'm going to defer to the  
9 clinician, and I'm going to ask Dr. Ginsberg again if  
10 he can make a comment to that effect.

11 DR. GINSBERG: Being a clinician, I would  
12 ideally design a clinical trial to address that issue,  
13 and I think the way it would be designed would  
14 probably be as a randomized trial, but as one arm what  
15 you would do would be to do the AcuTect and see  
16 whether or not, if the results are positive, you can -  
17 - and these are in patients with previous disease --  
18 if the results are positive, then you would do a  
19 confirmatory venogram to show that there's acute  
20 thrombus there.

21 If the results are negative, I would  
22 simply withhold anticoagulant therapy and insure that  
23 those patients did well in clinical follow-up.

24 So I think that the clinical trial is  
25 reasonably straightforward. The biology is a much

1 more problematic issue, but I would in a sense argue  
2 that the biology is secondary if the clinical trial  
3 dictates results that are consistent with good  
4 clinical practice.

5 DR. KONSTAM: Can I follow up on that  
6 though? I don't understand --

7 CHAIRPERSON RAMSEY: Dr. Konstam.

8 DR. KONSTAM: It's Mark Konstam.

9 I guess I'm not sure how you're defining  
10 acute venous thrombus. I haven't heard anything that  
11 clarifies that you have the ability clearly to make  
12 that distinction by venography, and there was  
13 variability in the duration of symptoms.

14 So, I mean, I think this is a very -- I  
15 mean, I don't see how. On what basis are you going to  
16 distinguish acute versus chronic?

17 DR. GINSBERG: Well, it's tricky in the  
18 sense that you don't have a reference standard, but  
19 what we do think is the following: that if you have  
20 a fresh intraluminal filling defect, that that's  
21 diagnostic of venous thrombosis.

22 So if you see that finding in the majority  
23 of patients who have a positive AcuTect, then I think  
24 it's reasonable to assume that the positive predictive  
25 value is high and that this test is diagnostic of

1 acute recurrent venous thrombosis.

2 On the other hand, if the test result is  
3 negative and the patient does fine in follow-up, I  
4 think as a corollary to that, you can assume that the  
5 negative predictive value for clinical events is high  
6 enough to avoid anticoagulant therapy.

7 So it's a mixed trial. You're looking at  
8 an anatomical test and a clinical outcome test.

9 DR. LINKS: Dr. Links again.

10 That trial wasn't done, and that's the  
11 conundrum. So help us out of the conundrum of the  
12 specific indication that Diatide wishes to label the  
13 product with, and what evidence do you need, and do  
14 they have that evidence?

15 DR. DEAN: Don't go away because I may  
16 need you.

17 CHAIRPERSON RAMSEY: Dr. Dean.

18 DR. DEAN: Yes. If you recall, in our  
19 discussions with the experts, this is obviously the  
20 conundrum, and everybody spots it right away. Really  
21 the best you can do here based on their advice to us  
22 is to take a patient for which this is the first time  
23 the disease has occurred in that patient, giving it a  
24 very high likelihood that it's acute, that there never  
25 was a previously existing condition, and then have the

1 entry criteria narrowed to a short window of time,  
2 like ten days.

3 So that's how we framed the trial to be  
4 able to capture the acute condition as best as  
5 possible, given all the difficulties associated with  
6 evaluating a physiological type test.

7 Would you concur?

8 DR. GINSBERG: Yeah, I mean, I think that  
9 makes good sense. It removes the confound of --

10 CHAIRPERSON RAMSEY: Dr. Ginsberg.

11 DR. GINSBERG: -- previous disease and the  
12 misinterpretation of previous disease.

13 I'm sorry.

14 DR. DEAN: She was just identifying you.

15 CHAIRPERSON RAMSEY: I'm just putting it  
16 in the record so that we know who's giving these  
17 responses. Sorry.

18 MR. MADOO: I'd also like to note for the  
19 record that the sponsor will be not voting, and they  
20 will not be contributing to the Committee consensus.

21 (Laughter.)

22 DR. DEAN: thank you.

23 CHAIRPERSON RAMSEY: Did we answer (b)?  
24 Is there sufficient mechanism of action information to  
25 support the potential to differentiate acute

1 thrombosis and acute phlebitis?

2 Dr. Hammes.

3 DR. HAMMES: Richard Hammes.

4 I think it's quite clear in terms of (a)  
5 that there's strong data that the apcitide binds to  
6 the receptor in question. Given though that in the  
7 inflammatory process of phlebitis, as it states,  
8 platelets are also found, and if these platelets are  
9 activated, they also will bind with apcitide.

10 And I think the high incidence of false  
11 positives that we've seen in the low specificity, it  
12 could well be a direct result of this. So given that,  
13 I don't think you can say that it doesn't go to  
14 endothelium, which gets us right into Part (b).

15 I see no evidence that you can differentiate  
16 acute phlebitis from acute thrombosis in light of that  
17 data.

18 CHAIRPERSON RAMSEY: Dr. Links.

19 DR. LINKS: A follow-up question to the  
20 FDA. With respect to the labeling, I think that the  
21 Diatide answers we just heard focused on sensitivity,  
22 and the comment that was just raised focused on  
23 specificity, and my question is: in guiding us for  
24 approvability of an indication, is it an issue of both  
25 sensitivity and specificity?

1           And by specificity I don't mean a normal  
2 group, but rather a group with a host of other  
3 diseases that may yield false positives in the context  
4 of the specific indication, or are we looking at  
5 sensitivity and normalcy rate, so to speak?

6           DR. LOVE: Some of that probably deals  
7 with another set of the questions which talks about  
8 labeling for proposed use. If you thought this was a  
9 screening agent, you might be more concerned about one  
10 aspect. If you thought this was a replacement or an  
11 alternative to contrast venography, then other issues  
12 become important. If you think it's an adjunct, other  
13 issues are important.

14           So I think that's all of what we'd like to  
15 hear you discuss and think about when it comes to  
16 labeling other product. Certainly we can label in  
17 pharmacodynamic sections of the clinical pharmacology  
18 portion of a label. We can put cross-reacting  
19 information there, but it would also affect perhaps  
20 some of the indications, and we have to think about  
21 that.

22           CHAIRPERSON RAMSEY: Comments?

23           DR. CHOYKE: Pete Choyke.

24           I'd just like to clarify at least on (b).  
25 You know, this isn't exactly pertaining to the

1 mechanism per se, but certainly from clinically the  
2 images that were shown, you should be able to  
3 differentiate between acute thrombosis and acute and  
4 the missing word is "superficial phlebitis" because  
5 the distribution is going to be quite different.

6 So, you know, it doesn't get to the issue  
7 of mechanism, but for me that's not so key because  
8 from a practical point of view, I think you will be  
9 able to differentiate that.

10 CHAIRPERSON RAMSEY: That was the message  
11 I got as well.

12 Any other comments? Dr. Kasper.

13 DR. KASPER: Yes, I had wanted to comment  
14 that I don't think it's all that important to  
15 distinguish acute thrombosis and acute phlebitis. I'm  
16 not sure that there's any way that we can. Even if  
17 one has a normal venogram, that doesn't mean that  
18 there isn't a little layer of thrombosis happening,  
19 and I think that it is not bad that some phlebitis  
20 were falsely positively diagnosed as thrombosis  
21 because the clinical reaction to that would probably  
22 be beneficial.

23 I don't think we can tell anyway.

24 CHAIRPERSON RAMSEY: Dr. Links.

25 DR. LINKS: In that regard, from a

1 clinical point of view could someone or a group of  
2 people please state the relevant clinical distinction  
3 and let's see what the evidence is for this agent  
4 based on that relevant clinical distinction or  
5 differentiation, whatever it is?

6 CHAIRPERSON RAMSEY: Dr. Jahnke.

7 DR. JAHNKE: Yes, Dr. Jahnke.

8 Well, certainly the treatment is  
9 different. Phlebitis is not necessarily treated with  
10 anticoagulation if there is no thrombosis. So the  
11 clinical treatment differs fundamentally.

12 If you feel that there is deep venous  
13 thrombosis, heparin followed by cumidization  
14 (phonetic) for treatment. If you feel it's an acute  
15 phlebitis, then rest, elevation, warm packs applied,  
16 et cetera. Perhaps anti-inflammatory agents are  
17 indicated.

18 So there is a clinical -- I feel not as a  
19 clinician; as a radiologist -- but there is a clinical  
20 difference in the treatment of those two entities.

21 CHAIRPERSON RAMSEY: I think we heard that  
22 they --

23 DR. JAHNKE: Not that they -- they don't  
24 usually coexist.

25 CHAIRPERSON RAMSEY: Ruth Ramsey.

1           And I heard that they can -- didn't we  
2 hear, I should say, that they can all look the same  
3 clinically? Thus, the idea is this would attempt to  
4 differentiate between them, not that I'm taking sides  
5 here.

6           Any other comments?

7           (No response.)

8           CHAIRPERSON RAMSEY: Okay. Let's move to  
9 two. The question: is there sufficient information  
10 to describe the imaging features that can distinguish  
11 positive and negative results for acute venous  
12 thrombosis?

13           There we are. We just talked about it.

14           MR. MADOO: Excuse me, Dr. Ramsey. So did  
15 we formulate any kind of consensus relative to these  
16 questions or are we going to be satisfied with just  
17 staccato comments or distinct comments?

18           CHAIRPERSON RAMSEY: Dr. Love?

19           DR. LOVE: I guess what I've heard -- I'm  
20 not sure that I hear a true consensus. What I've  
21 heard is that, yes, everyone seems to agree that there  
22 is preferential binding for the receptor, but there's  
23 still a potential for cross-reaction to the  
24 vitronectin, and a difference of opinion on whether  
25 that is or isn't clinically relevant.

1 I've heard one feeling that it doesn't  
2 matter, and perhaps we can handle it in labeling, and  
3 another opinion saying it does because it would affect  
4 treatment.

5 So I don't really hear a consensus on (b).

6 MR. MADOO: Does that, indeed, reflect the  
7 Committee's position?

8 I guess no comment would imply that that's  
9 the case?

10 DR. CHOYKE: No, I didn't hear the latter  
11 part.

12 CHAIRPERSON RAMSEY: Dr. Choyke.

13 DR. CHOYKE: That there was some clinical  
14 significance to the vitronectin reception. I mean,  
15 did anybody say that? Because I missed it.

16 DR. LOVE: No, I don't mean the  
17 vitronectin. I'm speaking now -- I'm sorry -- of the  
18 acute phlebitis and acute thrombosis.

19 DR. CHOYKE: Oh, oh, I see.

20 DR. LOVE: I'm sorry.

21 DR. AMENDOLA: This is Dr. Amendola.

22 I think that if we put in (b) the  
23 superficial phlebitis, my impression is that the agent  
24 does have the potential to differentiate thrombosis  
25 from phlebitis.

1 MR. MADOO: So would you care, Dr. Ramsey,  
2 to nutshell the Committee consensus for the record?

3 CHAIRPERSON RAMSEY: Well, I would just  
4 repeat what -- I'm sorry to mispronounce your name --  
5 but that there is sufficient data to support the  
6 potential to differentiate acute thrombosis and acute  
7 phlebitis, or to put it another way, is there  
8 sufficient, as they say here, is there sufficient data  
9 to support the potential to differentiate acute  
10 thrombosis and acute phlebitis?

11 Yes or no? Do we want to vote on that?

12 DR. KONSTAM: Can I just comment on that?

13 CHAIRPERSON RAMSEY: Certainly.

14 DR. KONSTAM: We're whispering in the  
15 corner. This is Marv Konstam.

16 There's a consensus in the corner here  
17 that maybe the question doesn't matter, and at least  
18 I'll give you my reason for thinking it doesn't  
19 matter.

20 The only thing that really matters here is  
21 if we're going to be able to identify a test that  
22 predicts outcome and that dictates management. Now,  
23 I think this could matter, the difference between  
24 acute phlebitis and acute thrombosis, but where I  
25 think it doesn't matter so much is because there's

1 also the issue of chronic thrombosis and acute  
2 thrombosis.

3 We're going to get into a significant  
4 degree of variation between the venogram and the scan  
5 results. We're going to try to presume from that that  
6 that has some implication about outcome, and I think  
7 that's really where the gist of the discussion is  
8 going to lie.

9 I mean, I think if it were clear, if this  
10 were the question, is it acute phlebitis versus acute  
11 thrombosis, then maybe we could answer yes, but for me  
12 I don't think it matters.

13 CHAIRPERSON RAMSEY: Any other comments?

14 Dr. August.

15 DR. AUGUST: We spent most of the morning  
16 hearing and seeing data that had to do with agreement  
17 and now we're being asked a totally different  
18 question. I don't think we were given enough  
19 information to allow us to answer Part (b) of that, to  
20 be perfectly honest with you, and I'm kind of confused  
21 at being asked in the first place.

22 There was no algorithm. There was no  
23 scheme of positives for this test and negative for  
24 that test that would enable us to make that  
25 differential. I think it's -- I personally think it's

1 not a fair question to pose to the Committee at this  
2 time.

3 DR. LOVE: Certainly we can understand and  
4 accept that. This question was relating really to the  
5 pharmacology information from the sponsor and from the  
6 agency in the beginning. This is not from the pivotal  
7 clinical trial. It's the baseline information.

8 CHAIRPERSON RAMSEY: Do you have enough  
9 response on the Committee?

10 DR. LOVE: Yes.

11 CHAIRPERSON RAMSEY: Thank you. You saved  
12 me.

13 Two, is there sufficient information to  
14 describe the image features that can distinguish  
15 positive and negative results for acute venous  
16 thrombosis?

17 Comments? Dr. Links.

18 DR. LINKS: There's some fantastic nuclear  
19 medicine physicians in the audience who have  
20 experience with this agent. I guess I'd love to hear  
21 from them because I suspect they've imaged patients  
22 who are not part of the trial who may end up  
23 addressing some of these other issues that we've just  
24 been discussing.

25 So I wonder if Diatide would like to

1 identify a couple to just give us some very quick  
2 information that goes beyond what we've already had  
3 presented.

4 CHAIRPERSON RAMSEY: I'm going to assume  
5 from the Committee that that's all right with the  
6 Committee to get the responses.

7 Please.

8 MR. MADOO: And, of course, with the  
9 proviso that for conflict of interest purposes any  
10 opinions will have to be characterized as being a  
11 Diatide consultant or otherwise.

12 CHAIRPERSON RAMSEY: Please identify  
13 yourself.

14 MR. PIPER: I'm Chris Piper.

15 We have Dr. Bob Caretta. He has been a  
16 clinical investigator on AcuTect studies.

17 DR. CARETTA: I'm Dr. Bob Caretta. I'm  
18 a community practitioner of nuclear medicine, and I've  
19 been involved in the Diatide trial, as well as other  
20 trials, and I've used I125 and I123 fibrinogen  
21 extensively when they were both available in the late  
22 '70s and early '80s to look at deep vein thrombosis,  
23 and I think this study is one of the best studies that  
24 we have to meet an unmet need, which is to find  
25 something that will show us an acutely forming

1 thrombus in a clinically suspect patient who is at  
2 high risk for the development of DVT and potentially  
3 pulmonary emboli.

4 The studies are relatively easy to ready  
5 for a qualified nuclear medicine physician, and they  
6 require only planar imaging. They don't require three  
7 dimensional or spec'ed imaging. They can be done  
8 relatively quickly, within the first 60 minutes or  
9 sooner with a positive study, and unlike some of the  
10 other agents that I have worked on, i.e., prostacint  
11 (phonetic), the monoclonal antibody for prostate  
12 cancer, and oncosin, the colorectal imaging monoclonal  
13 antibody, which require a high degree of training, a  
14 high level of skill, and a significant over read  
15 before you can feel comfortable in interpreting these  
16 images, I find that the AcuTect images are very, very  
17 easy to read.

18 Plus they can be read in patients who are  
19 trauma patients who have casts on their lower  
20 extremities because they have 140 kEV technetium gamma  
21 that comes through the calf. They can be read in  
22 patients who are bandaged who come out of surgery, and  
23 they are certainly an adjunct test, not a replacement,  
24 for Doppler ultrasound, but very, very useful when the  
25 ultrasound is either equivocal or negative,

1 particularly in the calf.

2 We don't do in community practice contrast  
3 venography anymore. You heard from Dr. Sostman this  
4 morning that at Duke they did approximately three to  
5 seven venograms out of 700 patients that they studied  
6 or so, and in community practice, no one does  
7 venography. It's all ultrasound, and we have a way  
8 now of simply, rapidly, and effectively imaging  
9 forming thrombi.

10 MR. MADOO: Excuse me, sir. You're  
11 attending this meeting on behalf of Diatide as a  
12 consultant?

13 DR. CARETTA: I am a clinical investigator  
14 for Diatide and here as a consultant, yes, sir.

15 CHAIRPERSON RAMSEY: Dr. Ponto.

16 DR. PONTO: I think we're all in agreement  
17 that there's this tremendous need that has to be met,  
18 and we've talked a lot about the disagreement in  
19 contrast venography, but I go back to the point that  
20 I made this morning.

21 In looking at the results that are  
22 presented for the AcuTect product, if you look across  
23 the six readers, there's a lot of disagreement,  
24 especially on the B study, but even in the A study,  
25 the number of positive reads ran from 48 to 56. The

1 number of positive reads on the B study went from 33  
2 to 78.

3 Why is there such a disagreement between  
4 the readers for the AcuTect images? Anybody.

5 MR. PIPER: Chris Piper.

6 We would like to respond to that. Dr.  
7 Rich Wahl, a consultant to Diatide.

8 DR. WAHL: Yeah. Richard Wahl, professor  
9 of internal medicine and radiology at the University  
10 of Michigan and Director of Nuclear Medicine Section  
11 there.

12 I've been involved in a lot of trials of  
13 new imaging agents, and I think perhaps what we need  
14 to reflect to are some of the comments Dr. Gottschalk  
15 made earlier this morning.

16 Imaging methods and even, in fact,  
17 histopathology are not perfectly reproducible from  
18 individual to individual. With pulmonary angiography,  
19 which has been in use probably for at least 30 years,  
20 the same individual looking at the same studies had  
21 about an 89 percent reproducibility rate.

22 When two individuals looking at similar  
23 sets of studies were compared, comparability was about  
24 80 percent. Those are with a study that's been in  
25 practice and in their practice for probably their

1 entire careers, where they have a lot of experience  
2 with it.

3 The situation here, as I understand it, is  
4 that the degree of concordance among readers was  
5 around 60 percent, which is lower than the 80 percent  
6 seen for pulmonary angiography, but I think you have  
7 to consider the 60 percent was based on a limited  
8 training set, a finite number of cases, with no prior  
9 experience with the methodology.

10 So as the readers would read more, it  
11 would be expected that concordance rates and  
12 reproducibility would increase. So I don't find the  
13 figures that shocking or surprisingly low. I think  
14 that they're actually pretty good, considering it's a  
15 brand new test, and the readers, even though there  
16 were three readers, there would have been limited  
17 experience among the readers.

18 So it's a new test, limited experience, a  
19 majority concordance rate, and even with our most  
20 supposedly gold standard tests, we don't have perfect  
21 concordance, as we've seen with venography.

22 So I think that would be at least an  
23 explanation.

24 DR. KONSTAM: Marv Konstam.

25 You know, I guess getting to the question,

1 I have a lot of trouble with this question because I  
2 don't see how we can answer in the affirmative that  
3 there is sufficient information to describe the image  
4 features that can distinguish positive and negative  
5 results, you know, until and unless we decide that we  
6 have some positive data and that we have sufficiently  
7 positive data against something that we consider  
8 approximating a gold standard.

9 And I don't know how -- I think we're  
10 going to have to get to that question because that's  
11 going to be the key.

12 If the answer to that question is no, then  
13 the answer to this question certainly is going to be  
14 no. I think if the answer to that question is yes,  
15 then I guess, yes, the sponsor did come forward with  
16 a set of criteria. I don't think we can tell, based  
17 on what I understand from the FDA presentations. I'm  
18 not sure we can tell to what extent the readers stuck  
19 to those criteria.

20 But, you know, if we agreed that we had  
21 some positive results, then I suppose we could accept  
22 the sponsor's set of criteria since they trained their  
23 readers. That might be possible.

24 But, I mean, I just think we have to first  
25 decide whether we have a positive set of results or

1 not.

2 CHAIRPERSON RAMSEY: Yes, D'Agostino.

3 DR. D'AGOSTINO: I guess I sit here with  
4 some amazement that, you know, in other fields part of  
5 the judgment of whether or not you have a successful  
6 trial is whether or not different readers could  
7 produce the same result, and was it a lack of training  
8 and so forth? But I don't think that from what we've  
9 been told that we have information that can  
10 distinguish the positives from the negatives. I don't  
11 think we have information if you push it too far that  
12 we even know if we have positives, as you're saying,  
13 and I would presume that part of a clinical trial  
14 would, in fact, worry about the agreement of the  
15 raters and judge it on that.

16 And then once we say we have enough  
17 agreement among the raters, then see where the  
18 positives and negatives differentiate, and I would  
19 think that the answer should be no here based on what  
20 we heard this morning.

21 CHAIRPERSON RAMSEY: Dr. Hammes.

22 DR. HAMMES: Richard Hammes.

23 I recall reading in the packet here  
24 something about a region of interest analysis on these  
25 studies, but I didn't hear anything about that today.

1 Is this some sort of quantitative analysis? It would  
2 be very helpful if it was, and if it wasn't, could it  
3 be done?

4 But quantitative data would answer a lot  
5 of these.

6 CHAIRPERSON RAMSEY: Comments from the  
7 manufacturer?

8 DR. NICODEMUS: Yeah, we have -- Dr.  
9 Nicodemus from Diatide -- we have results here from  
10 one of the Phase II studies looking at region of  
11 interest ratios with different doses of radioactivity,  
12 and as you can see, looking at the 20 millicurie dose  
13 reactivity, which is what we are recommending, the  
14 region of interest ratio is 1.6.

15 I was wondering if Dr. Wahl would like to  
16 comment on a ratio of 1.6 and the clinical  
17 significance of that.

18 DR. WAHL: I didn't draw these regions of  
19 interest, but I believe that these represent region of  
20 interest and symmetrical areas with the question of  
21 whether the clot is present or not.

22 Again, I'm Dr. Wahl from Michigan.

23 So what you're looking for is between the  
24 mean value and 1., basically one. So as a physician  
25 when you look at these, you look at a number of

1 things.

2 Dr. Wyland has a lot of experience with  
3 this, but looking only numerically would not be the  
4 typical approach to doing an interpretation of a scan.  
5 So I think we know a lot about where clots occur in  
6 the legs, and looking to see if the hot spots are  
7 linear and in the expected anatomic location of veins  
8 is very reasonable, for starters.

9 Similarly, if you're trying to see deep  
10 venous thrombosis and you're looking at something  
11 superficial on the scan, that that logically wouldn't  
12 be deep venous thrombosis.

13 So interpretation involves prior knowledge  
14 of disease processes, and then seeing if the scan  
15 pattern is consistent with where you know the  
16 pathophysiology would be expected to occur.

17 As far as these ratios, the better the  
18 test, the higher the ratio between the affected and  
19 unaffected site. So ratios, let's say, mean ratios of  
20 1.3 to 1.4 would probably be useful depending on what  
21 the variance is. We can see that the standard error  
22 would be reasonably low. A ratio of 1.6 at the 20  
23 millicurie ratio would be a pretty substantial ratio.

24 As an example, when we do lung perfusion  
25 activity ratios in trying to decide if a lung can be

1 removed or not, our maximum differences are often in  
2 the 20 to 40 percent range between lungs, but on that  
3 kind of data, we make decisions on which lung should  
4 be surgically removed.

5 So this degree of difference is not  
6 insubstantial, but I would think it would not be the  
7 only thing used to make a diagnosis.

8 DR. KONSTAM: No, I mean the issue of  
9 split lung function. I mean, there -- this is Marv  
10 Konstam -- I mean, there you're looking for a  
11 physiologic difference between two lungs. You're not  
12 attempting to make an anatomic diagnosis.

13 I mean, this, I think, if I understand you  
14 correctly, you're taking to suggest that there might  
15 be some degree of accuracy in making a diagnosis that  
16 there is pathology present. You know, these ratios  
17 seem awfully -- maybe I don't understand them enough,  
18 but they seem awfully low to me. They seem awfully  
19 close to unity for ability to say with certainty that  
20 you have or don't have pathology.

21 DR. WAHL: Well, I think, as I indicated  
22 earlier, that you wouldn't -- the typical nuclear  
23 physician would not use ratios alone, nor would a  
24 radiologist use a numerical Hounsfield unit in  
25 general to make a diagnosis. Some of the visual

1 findings have to be consistent with the numerical  
2 values.

3 So I would think that these would be  
4 adjunctive to the pattern, but if they are  
5 representative of an asymmetry between sides and the  
6 side that has the abnormal pattern also has 30 to 40  
7 percent more accounts or 50 percent more accounts than  
8 the other symmetrical region of interest, that would  
9 certainly support there being -- obviously there's  
10 deposition of Technetium there and presumably by the  
11 pathophysiological mechanism.

12 Just not to belabor it, but other  
13 processes we look at in nuclear medicine all the time,  
14 such as -- well, we do quite commonly sacroiliac joint  
15 uptake ratios looking for sacroiliatis, and the  
16 differences between sides can be in the range of 25 to  
17 30 percent, and depending on how many counts you get,  
18 the confidence intervals on those can be pretty tied.

19 DR. KONSTAM: Are the background  
20 subtracted numbers or not?

21 DR. WAHL: I didn't personally draw the  
22 regions, but I'm being told that that is correct,  
23 which would be, of course, the appropriate -- well, I  
24 think that would be an appropriate way to do it.

25 DR. KONSTAM: Right, but I defer to you or

1 to other nuclear medicine specialists here, but the  
2 ratios seem low, particularly if your background is  
3 subtracted.

4 DR. WAHL: But I would say, again, that  
5 they're not that low relative to other procedures we  
6 do and not interpreted in a vacuum.

7 CHAIRPERSON RAMSEY: Dr. Links.

8 DR. LINKS: A question of clarification on  
9 this whole issue of variability and how we as a  
10 Committee want to deal with it.

11 It seems to me that historically if you  
12 look at validation of any new technique where you have  
13 individual reader's data and then a consensus or  
14 aggregate, majority read, however you want to call it,  
15 that in the early stages of technique development, the  
16 first introduction of the technique, that the  
17 consensus or aggregate or majority read is always of  
18 higher accuracy than any of the individual readers  
19 alone.

20 And typically in the literature that's the  
21 numbers on which you initially judge the performance  
22 of the technique, and I'm just wondering here because  
23 this morning there was a specific question about  
24 whether or not we should focus on the individual  
25 reader's performance or the aggregate/majority

1 performance.

2 And my own philosophy would say, hey, it's  
3 a new technique. The aggregate performance is must  
4 representative of what, once it disseminates into the  
5 field and there's adequate training and use, what it  
6 will be.

7 But I want some guidance. What should we  
8 be focusing on, individual readers, both performance  
9 and variability amongst them, or concentrate on the  
10 aggregate?

11 CHAIRPERSON RAMSEY: I don't want to be  
12 silly, but is that what we're talking about now? Is  
13 that in this?

14 DR. LINKS: It's relevant to this because  
15 it has to do with the variability in the AcuTect  
16 interpretation across readers, which has to do with  
17 both the criteria for how to interpret it and the  
18 reliability of those criteria.

19 CHAIRPERSON RAMSEY: Dr. Choyke.

20 DR. CHOYKE: Well, you know, my approach  
21 to that would be that it's really the aggregate that's  
22 most important because it averages out all of these  
23 different points on an ROC curve basically.

24 But what it points out to me, I mean, when  
25 you see numbers that are 60 percent agreement and that

1 kind of thing, you know that what was missing here was  
2 a training set, you know, a real 20 patients where you  
3 were given feedback and then you could refine, and you  
4 were told what other people in the group did, and then  
5 you were able to refine your diagnostic criteria and  
6 converge on a number.

7           You know, clearly, there's got to be  
8 training involved with this like any other test, and  
9 that's the missing element. I mean my impression is  
10 that in these tests they were never really given a  
11 training set beyond what we saw and the ability to  
12 really get into what the group felt, you know, was the  
13 right answer. So that's why you have these  
14 variabilities.

15           That's why I sort of focused on the  
16 aggregate response.

17           CHAIRPERSON RAMSEY: Dr. Kasper and then  
18 Dr. D'Agostino.

19           DR. KASPER: I think that we are now on  
20 Roman numeral two, and I'd like to say that this is an  
21 anatomic diagnosis, and many things in radiology and  
22 in pathology depend on the experience of the  
23 radiologist/pathologist doing it. The more they do of  
24 that particular area, perhaps the more experience, the  
25 better the result is, and we don't really have and we

1 may never really have absolutes that we can use to  
2 describe the image features.

3 I think we have generalities to describe  
4 the image features, and often that's where we are in  
5 certain radiologic and pathology situations. So I  
6 don't think we need perfection here or anything near  
7 it, but general guidelines.

8 CHAIRPERSON RAMSEY: Dr. D'Agostino.

9 DR. D'AGOSTINO: I don't know if you're  
10 referring to me, but I certainly asked that question  
11 this morning about how many should we be looking at.  
12 I expected the answer to come back: look at the  
13 aggregate and don't bother with the individuals. I  
14 was kind of surprised. I thought that was going to be  
15 an issue that we could put to rest by that question,  
16 but it turned out that it went the other way.

17 I think the aggregate is clearly the right  
18 thing to do, but I think the question that's here is  
19 that we don't have information. Even if we take the  
20 aggregate, if there's negatives being stated, my sense  
21 is from the presentations we don't have a lot of  
22 information on the features that made it negative and  
23 so forth.

24 I think that's the question that's being  
25 asked here, is it not? It isn't so much that if we

1 believe it's positive, we believe it's a negative.  
2 There's information on the positives, but we've run  
3 out of information on the negatives, and that's the  
4 type of question I thought we were responding to here.

5 CHAIRPERSON RAMSEY: Dr. Jones.

6 DR. JONES: I wanted to -- is this live?

7 I wanted to make comment with regard to  
8 Peter Choyke's observation about a training session.  
9 There were -- actually the company did have at least  
10 20 cases presented to the trainees, but I don't think  
11 they assessed the trainees' response to see if they  
12 were uniform or if the actual consensus among the  
13 trainees was occurring. There was a cadre of at least  
14 20 patients in the training session.

15 CHAIRPERSON RAMSEY: Dr. Love, have you?

16 DR. LOVE: Well, just commenting on the  
17 last comment from Dr. D'Agostino was part of what's  
18 behind this question, yes, the lack of the other  
19 information on the negative side and whether or not  
20 it's relevant at this point.

21 CHAIRPERSON RAMSEY: I'm not sure we  
22 answered that. Did we answer it? No. Okay.

23 Let's move on anyway. All right. We'll  
24 go to 3(a). Now we're back to the Hamilton -- oh,  
25 sorry.

1 DR. LOVE: Actually, depending on what  
2 your recommendations are in the long run, just a  
3 little bit more on this one.

4 Are we to interpret your comments then as  
5 saying the package insert or training sessions would  
6 be labeled in a manner that was consistent with the  
7 information that was given during the training  
8 sessions to identify what is positive on an image, but  
9 what would be a negative finding? That's the  
10 question.

11 In other words, you can interpret --

12 CHAIRPERSON RAMSEY: I guess if it doesn't  
13 meet the criteria for being positive.

14 DR. LOVE: I mean it's the opposite. It  
15 means it isn't there.

16 CHAIRPERSON RAMSEY: That's right.

17 DR. LOVE: But I just want to make sure  
18 that what I hear you saying is that if the  
19 recommendations for interpreting positive are  
20 followed, then that would be sufficient to distinguish  
21 a positive or a negative. Is that what the Committee  
22 is saying?

23 CHAIRPERSON RAMSEY: I would certainly  
24 like other comments.

25 CHAIRPERSON RAMSEY: Dr. August.

1 DR. CHOYKE: Well, I heard during that  
2 brief training session that they described the normal  
3 as symmetrical activity in the leg, and that seemed  
4 pretty good to me, and the images showed -- you could  
5 just see the faint glimpse of a femoral vein and the  
6 other veins. If that activity was symmetrical, side  
7 to side, that was a negative, and that seemed clear.

8 DR. LOVE: Right. There were four  
9 criteria specified and also criteria for whether or  
10 not you had multiple times, and it's just the question  
11 that Dr. D'Agostino was mentioning.

12 We have the information that says you read  
13 it as positive if you see these things. Case report  
14 forms identified information to confirm those items if  
15 it was read as positive. You didn't have similar  
16 information if it's read as negative.

17 So it's just pressing the point on how you  
18 would want to see a package labeled if this is your  
19 recommendation.

20 CHAIRPERSON RAMSEY: Dr. August.

21 DR. AUGUST: Isn't it axiomatic that  
22 something is negative if it lacks the criteria that  
23 make it positive? I mean this is not rocket science.

24 (Laughter.)

25 DR. KONSTAM: Right. This is Marv

1 Konstam.

2 And I understood for positivity, unless I  
3 understood wrong, it required that all of the criteria  
4 be met, that is, asymmetric, central, what else? What  
5 were the other two? Linear. What was the fourth?

6 DR. LOVE: And what you have to do if you  
7 push the gain all the way up.

8 DR. KONSTAM: Oh, on two views, on two  
9 views.

10 PARTICIPANT: Two time points.

11 DR. KONSTAM: Oh, two time points, at two  
12 time points.

13 Okay. So if it didn't meet any of those,  
14 if there was one of those criteria that it didn't  
15 meet, then it's negative, right? Right.

16 DR. D'AGOSTINO: Can I ask a question?

17 CHAIRPERSON RAMSEY: Yes.

18 DR. D'AGOSTINO: There's so much  
19 disagreement it must not be -- maybe it is rocket  
20 science, but not all of the negatives came out the  
21 same way. I mean some that were negative by one,  
22 declared positive by another. So you can't say that  
23 it was obvious that you had a checklist that made it  
24 positive. There's something that made some people say  
25 negative and others say positive to the same thing.

1 DR. KONSTAM: This is Marv Konstam again.

2 I believe the reason we're struggling is  
3 because these results are so marginal at best. I  
4 mean, as we get forward, if there were a clear gold  
5 standard and if we were at 90 percent agreement, then  
6 we wouldn't be debating about whether or not the  
7 people who were trained strictly followed the  
8 training. We would know they were trained. We would  
9 know what criteria they were handed, and we would  
10 assume, well, they must have followed it because they  
11 all got it right.

12 The reason we're struggling with this is  
13 because a lot of times they didn't get it right, and  
14 we're not sure who got it right. So in that context  
15 I don't think we know what's going on.

16 CHAIRPERSON RAMSEY: Okay. Thank you.

17 Let's move on to 3(a), back to the  
18 Hamilton data and whether we can look back. I don't  
19 want to bias my statement here, but let's see. I have  
20 a note.

21 Why did we accept the Hamilton data post  
22 hoc, as it were, when it is not the way we usually  
23 would look at data? And that's the question, and  
24 would we accept then what we did to come to the final  
25 conclusion?

1 Is that what you're trying to --

2 DR. LOVE: No. Depending upon your  
3 results, that's just something I just wanted to make  
4 sure we could hear, the issues and thoughts that are  
5 behind your recommendations.

6 DR. LINKS: That assumes we do accept it.

7 DR. LOVE: No, whichever. I'm saying  
8 if -- the reason obviously if the -- Biometrics and  
9 most of the offices generally do not -- are generally  
10 concerned about retrospective post hoc analyses, and  
11 generally if we were going to accept that, we'd need  
12 a very clear reason for why in order to make  
13 prospective policy decisions, and that's why I'm  
14 asking for clarification behind your recommendations,  
15 whichever they might be.

16 CHAIRPERSON RAMSEY: Comments? Dr. Links.

17 DR. LINKS: This is maybe a semantic  
18 quibble, but in an epidemiologic sense whether you  
19 collect the data and then analyze it or analyze it as  
20 you're collecting it, that's not the distinction  
21 between retrospective and prospective.

22 So using the Hamilton data may be post  
23 hoc, but it's actually no more retrospective than if  
24 you had used the blind data. It's a quibble, but it's  
25 an important point because we're pejoratively labeling

1 the Hamilton as being retrospective, when in fact it's  
2 not epidemiologically.

3 My own personal opinion is that even  
4 though I fully understand what Dr. Welch said earlier,  
5 it sounded very logical. Philosophically I disagree.  
6 I don't think -- I think if you're comparing  
7 something, you compare to the best thing you have to  
8 compare it to, and there's no reason in the world why  
9 Diatide, in my opinion, should be penalized for  
10 variability in venography interpretation. You go to  
11 the best interpreters you can find, and if there's  
12 only one group you can trust, use them for both  
13 studies A and B.

14 And so my own personal feeling is that in  
15 the context of independence, that A and B are  
16 adequately independent, and as I say, I don't think  
17 they're retrospective.

18 CHAIRPERSON RAMSEY: Dr. Konstam.

19 DR. KONSTAM: Marv Konstam.

20 You know, I mean, I think I just would  
21 continue Ralph's discussion of this earlier because I  
22 think he said what I feel about this.

23 I think you can take your pick, as far as  
24 I'm concerned, about which way to go. I think you can  
25 stick to the prespecified analysis as it was described

1 in the protocol and stick with the first set of  
2 reviewers that the sponsors chose, which I consider  
3 the primary analysis of the study.

4 If you do that, you don't have a positive  
5 study.

6 Now, in terms of what's right, I'm willing  
7 to accept that retrospectively it makes more -- they  
8 should have chosen the Hamilton reviewers. I would  
9 say they should have done that to begin with. They  
10 didn't. Now, what do we do?

11 And I think the issue really is what Ralph  
12 said. We don't know what to do with those because we  
13 don't know how to interpret them statistically. I  
14 would feel strongly that on a statistical basis, there  
15 is some unknown penalty that the study has to suffer  
16 from changing its analysis, and we don't know what  
17 that is. We don't know how to do that.

18 And I think, you know, to me, again, I  
19 think if it were 95 percent agreement I might not  
20 worry about what the statistical test was, but we're  
21 talking about, you know, marginal agreement, to begin  
22 with, or marginal level of acceptable agreement and an  
23 uncertain gold standard.

24 So I think it's going to wind up accepting  
25 a penalty that is going to put it into no man's land.

1 CHAIRPERSON RAMSEY: Any other comments?  
2 Dr. Choyke. Oh, sorry. Dr. Jahnke.

3 DR. JAHNKE: Yeah, I think we mentioned it  
4 -- again, Dr. Jahnke -- we mentioned it a few times,  
5 and the company pointed out that they did not  
6 capriciously decide to discard or not emphasize Study  
7 32A. It was because of the very high positive rate,  
8 you know, the 80, 90 percent, 82 percent, which was  
9 much higher, double the expected rate of positivity of  
10 venography in a typical group of patients, which is  
11 stated to be in the 30 to 40 percent range.

12 So it was done with good motives at least  
13 in some science mind.

14 CHAIRPERSON RAMSEY: Dr. Choyke?

15 DR. CHOYKE: I'd just like to reiterate  
16 what Dr. Links said about the issue of penalizing the  
17 sponsor here for a problem with venography, which  
18 clearly has problems with reproducibility, all the  
19 problems we are condemning AcuTect for:  
20 reproducibility, interobserver variability, that kind  
21 of thing.

22 And, you know, I think that we have to be  
23 careful about, you know, where do we go from here  
24 except to recommend some very elaborate outcomes  
25 study, which probably should be done down the line,

1 but other than that we don't have truth. It's going  
2 to be very difficult to get truth in this study, and  
3 repeating it won't get there. Basically we're stuck  
4 with the data that we have, I think, and I think the  
5 best you can do with it is interpret it with the  
6 experts that have seen the most.

7 CHAIRPERSON RAMSEY: Dr. D'Agostino.

8 DR. D'AGOSTINO: Yeah. I guess I'm not  
9 sure why we're stuck with the data we have. This is  
10 not a four million subject study that will take 27  
11 years to perform. It's a study that can be  
12 replicated, and I wouldn't want to replicate it. It  
13 can be a study that can be done where you, in fact,  
14 have the readers trained appropriately at the  
15 beginning so that you don't run into this  
16 retrospective or post hoc, which is probably a better  
17 word for it, analysis that you have to interpret.

18 And, you know, we all have different  
19 experiences, but the experiences that I see all the  
20 time is that we see the retrospective studies when  
21 they turn out to say what we want them to say, and we  
22 don't see all those retrospective studies that turn  
23 out to be negative.

24 I mean this was a re-analysis of the data,  
25 and it turned out to be positive. I don't know, and

1 I said it before, but I don't know how to interpret if  
2 this could be reproduced one more time, and I think,  
3 again, if the data were so striking that I would be  
4 willing to say, "God, what am I say?" but I don't  
5 think this data is so striking. I think it's  
6 marginal, and I think that there are so many questions  
7 with trying to buy into the post hoc procedure that we  
8 shouldn't do it.

9 CHAIRPERSON RAMSEY: I think we'll move on  
10 to the next question.

11 Is there sufficient information from the  
12 agreement of AcuTect and contrast venography results  
13 to develop labeling recommendations for clinical use?

14 That's a big leap, I know. Dr. Love, do  
15 you want to make any comments at this point?

16 DR. LOVE: This question has to do with  
17 some of the things you talked about earlier. The  
18 false positive/false negative agreement gives you some  
19 information about overall agreement in the diagnostic  
20 arena, but not necessarily the positive/positive,  
21 negative/negative issues that have been discussed.

22 So given those kinds of issues, do you  
23 feel that the data would allow you to make  
24 recommendations for use, screening?

25 CHAIRPERSON RAMSEY: I guess we might

1 throw that back to you, if you've heard enough.

2 DR. LOVE: Or you may want to -- you could  
3 also look at this one after you answer the  
4 approvability question.

5 CHAIRPERSON RAMSEY: That's what I was  
6 thinking. We might come back to some of these when we  
7 have a little more discussion. So let's do that for  
8 now. Let's skip that one. I'll put it in the back of  
9 our minds and go on to (c)(1).

10 Do you recommend accepting Study 280-32A  
11 as one of the pivotal studies to demonstrate the  
12 efficacy of AcuTect for scintigraphic imaging to  
13 detect acute venous thrombosis?

14 And the corollary to that is: do you  
15 recommend accepting -- let's take those together --  
16 282-3B as one of the two pivotal studies?

17 Dr. Links.

18 DR. LINKS: A question of clarification.  
19 If we do so, which standard are we using, the blind  
20 read, the clinical read, or the Hamilton read?

21 DR. LOVE: Right. That's Question (a).  
22 Which one do you recommend? Maybe a little bit  
23 more -- I think I heard most people around the table  
24 say take the Hamilton read, but not necessarily  
25 everyone.

1                   For us it would help us to get a clearer  
2 answer on (a).

3                   CHAIRPERSON RAMSEY: I guess that's what  
4 I heard, is to take the Hamilton read, but I would  
5 like comments from the committee members.

6                   Dr. Kasper.

7                   DR. KASPER: I think I'd agree with Dr.  
8 Links that that seems to be -- that is the -- the  
9 Hamilton read is the read done by the people who are  
10 the very most expert, but I certainly would like to  
11 see in any publication all the reads because we've  
12 learned something from this.

13                   We've learned the variability of readers,  
14 and we've learned the degree of imperfection of the  
15 venography.

16                   CHAIRPERSON RAMSEY: Other comments?

17                   Dr. Hammes.

18                   DR. HAMMES: I think there's probably a  
19 consensus to use the Hamilton read for the most part.  
20 What I see in this specific question here, if we throw  
21 out the first blinded read because it had 80 percent  
22 positive as one of the FDA reviewers brought up,  
23 shouldn't we throw out the A study because it only had  
24 20 percent in the Hamilton read? And that's a dilemma  
25 to me that I haven't really reached a decision on.

1 CHAIRPERSON RAMSEY: Other comments?

2 Dr. D'Agostino.

3 DR. D'AGOSTINO: It's not an upsetting  
4 decision when you have a particular study and you have  
5 two reads that both give you the same result. I just  
6 -- when we say the Hamilton we say it because on  
7 absolute criteria we believe it's better than the  
8 procedure that was used in the study, but there's a  
9 merit in looking at Study A to say that it was  
10 designed in a particular fashion, and it did on its  
11 own implementation come out with a positive result.

12 There is also a Hamilton read for that  
13 study which doesn't contradict that result, but if we  
14 say that we accept A because of the Hamilton read,  
15 then what we're saying is that we are accepting the  
16 study that deviated, for reasons that deviated from  
17 the original protocol, and I'm not sure we have to buy  
18 into that for acceptance of A.

19 I think in terms of what the next study  
20 should look like, in terms of what we think is the  
21 better reading, we can say Hamilton, but we can take  
22 A on its own merits, I think. Unless I'm missing  
23 something, A was a positive study.

24 CHAIRPERSON RAMSEY: Dr. Konstam.

25 DR. KONSTAM: Marv Konstam.

1           Yeah, Ralph. I'm not sure I'm there  
2 because the question, I think, as appropriately stated  
3 is: do we consider one of two pivotal studies to  
4 demonstrate the efficacy of AcuTect for scintigraphic  
5 imaging to detect acute venous thrombus? And I think  
6 that's the question. I think that's the right  
7 question.

8           And in that context, I can't come to the  
9 conclusion that it is. I think I can accept the fact  
10 that it is a positive study based on its hypothesis  
11 and based on a reasonable statistical analysis, but I  
12 think that all we're left with, you know, as  
13 clinicians at the end of the day is that we've shown  
14 that there is at least 60 percent agreement with  
15 venography. That's what the study showed.

16           Now, I mean, I agree with the comments  
17 that we shouldn't penalize the company because of the  
18 problems of contrast venography. I don't want to  
19 penalize anybody. The question I'm left with is:  
20 what do we know from this study that is going to help  
21 a clinician?

22           And I think if all we know from the study  
23 is that there's at least a 60 percent agreement with  
24 contrast venography, that's not helpful to me as a  
25 clinician.

1 DR. D'AGOSTINO: Yeah, I was talking about  
2 the Hamilton versus the non-Hamilton, and I guess I  
3 was glibly saying that we could take it as a positive  
4 study. I think it's a positive study for how it was  
5 designed. Whether or not it's a useful study is the  
6 question you're raising, which I thought we'd get to  
7 when you talk about the approvability.

8 CHAIRPERSON RAMSEY: Dr. Choyke.

9 DR. CHOYKE: Pete Choyke.

10 I'd like to suggest that you ask for the  
11 data from these two studies that has clear positives  
12 and clear negatives, that is all readers agreed that  
13 the venograms were positive and the venograms were  
14 negative. It will be a small subset of your  
15 population, but let's face it. If we have significant  
16 disagreement with that data set, we're in big trouble.  
17 If we have significant agreement in that set, at least  
18 we know we're on the right track, and you know, your  
19 confidence about approval would be greatly enhanced,  
20 I think.

21 DR. LOVE: What you're asking then is all  
22 readers -- are you including the open venogram read as  
23 well or the two blinded reads?

24 DR. CHOYKE: You could do it any way you  
25 wanted to.

1 DR. LOVE: Okay.

2 DR. CHOYKE: But, you know, basically you  
3 have a very nice data set now. You should have all  
4 the data from 240 patients, and you have a zillion  
5 readers now. So you could really get unanimity of  
6 opinion.

7 DR. LOVE: Okay. You're making a  
8 recommendation. That's why I'm --

9 DR. CHOYKE: Yes.

10 DR. LOVE: -- pressing it. You're saying  
11 take the data set and see where all venogram reads  
12 agree, look to see whether the AcuTect read is the  
13 same.

14 Are you concerned about potential sample  
15 size issues? Let's say it turned out to be 20  
16 patients. I'm pressing on purpose so that I can  
17 understand what it is you want us to do.

18 DR. CHOYKE: Well, that tells you  
19 something if you only have 20 patients. I mean I  
20 think we're really in trouble here if out of all these  
21 reads only 20 agreements are found.

22 I mean I'm expecting something like 30  
23 percent of the cases will agree or 40 percent. I  
24 mean, I sure hope the negatives will agree with each  
25 other more than that.

1           So I don't really think you're going to  
2           have 20, only ten percent.

3           DR. LOVE: Right.

4           DR. CHOYKE: But you might.

5           CHAIRPERSON RAMSEY: Dr. Konstam suggested  
6           possibly we might want to vote on (c)(1) and (2); is  
7           that correct?

8           And I would just ask Dr. Love if you feel  
9           that you need a vote on those or do you have a flavor  
10          of --

11          DR. LOVE: That would be -- this is an  
12          important question. A vote would be fine.

13          CHAIRPERSON RAMSEY: Dr. Ponto.

14          DR. PONTO: Isn't the question here  
15          whether these are pivotal studies or not, whether we  
16          accept them as a study, not whether we're accepting  
17          the results as being positive or not?

18          DR. LOVE: Oh, maybe this is a little bit  
19          of our jargon here. When we say do you accept it as  
20          one of the two, yes, it implies a positive outcome.  
21          So it would be substantial.

22          DR. D'AGOSTINO: Can I ask?

23          CHAIRPERSON RAMSEY: Yes.

24          DR. D'AGOSTINO: So then in answering  
25          this, we have to get to the question of whether or not

1 we think the study with the 60 percent and so forth  
2 made sense.

3 PARTICIPANT: I don't want to vote.

4 (Laughter.)

5 DR. LINKS: And another question of  
6 clarification in that regard. The way the question is  
7 worded it says "to detect." That to me sounds like a  
8 sensitivity question.

9 DR. LOVE: That's not implied.

10 DR. LINKS: Okay.

11 DR. LOVE: It's basically for the  
12 indication as proposed.

13 CHAIRPERSON RAMSEY: Well, Committee, do  
14 we want to vote? Do you want to go through all of the  
15 discussion and come back and vote on that?

16 I would actually prefer that. It might --  
17 as I sit here, I'm not perfectly clear in my own mind  
18 what I would want to say, and it might clear it up,  
19 and it might not. So let's go forward with the  
20 understanding that we will come back and vote on these  
21 two.

22 Four is safety. Is there sufficient  
23 information to support the safety and reasonable  
24 labeling of AcuTect?

25 Comments?

1 DR. CHOYKE: Pete Choyke.

2 I think that this is pretty much as safe  
3 as any drug that I've ever seen. So --

4 CHAIRPERSON RAMSEY: Well, that's a pretty  
5 good comment. Any other comments?

6 Dr. D'Agostino.

7 DR. D'AGOSTINO: Do we -- and I'm  
8 deferring the question, but I'm raising it -- do we  
9 have to worry about no information after the three  
10 hours basically? We have three hour information and  
11 then some sort of global information that one day, but  
12 is there a concern? I'm just asking that question.

13 DR. KONSTAM: Yeah, I guess I'd follow up  
14 on that. I just wanted to ask Peter to follow up on  
15 his comment because we heard the FDA safety reviewer  
16 saying he was not satisfied with the amount of safety  
17 data that he had.

18 So I'm concerned about that. So could you  
19 comment on why you don't agree with that?

20 DR. CHOYKE: There were 169 patients who  
21 were followed at 24 hours, and it was still less than  
22 one percent side effects, and you know, I don't really  
23 know this for a fact, but I suspect that if you don't  
24 see anything in three hours, if you see less than one  
25 percent in three hours, the chances that you'll start

1 developing, especially from a peptide agent, things at  
2 24 hours when it's long excreted, I just don't see  
3 that as a big concern.

4 CHAIRPERSON RAMSEY: Any other comments?

5 DR. KONSTAM: Well, I mean, I just wonder  
6 whether we ask Dr. Zolman, who raised this concern,  
7 what would he like to see in an expanded safety data  
8 set.

9 DR. ZOLMAN: We would probably like to see  
10 about 600 patients.

11 DR. KONSTAM: Pardon me?

12 DR. ZOLMAN: We would probably like to see  
13 up to 600 or 1,000 patients. Otherwise this would  
14 have to be particularly treated as a different  
15 situation in labeling. In other words, it wouldn't be  
16 a standard labeling.

17 DR. LOVE: Numbers of sample sizes vary.  
18 You know, there are a lot of different ways to  
19 approach it. For repeat dosing the figures that Dr.  
20 Zolman mentioned are often quoted in ICH guidelines,  
21 but such don't exist for single doses, and we've  
22 certainly approved products with smaller numbers than  
23 that certainly.

24 But I think the issue here is sometimes  
25 it's not so much what's the actual number. You know,

1 there are tables you can look at to try to figure out  
2 how many patients do you need to try to be able to pick  
3 up an adverse event with a certain degree of  
4 likelihood that occurs, say, at one percent, two  
5 percent, .5 percent.

6 It's often very difficult in a single dose  
7 trial to make those assessments.

8 Normally what we would like to see is at  
9 least a larger data set that is monitored out to 24  
10 hours. We certainly balance that with pharmacokinetic  
11 data where the excretion rates, whatever else might  
12 have been seen in preclinical data.

13 I think part of the concern is that some  
14 things can't be detected at three hours, and what do  
15 we do about that?

16 CHAIRPERSON RAMSEY: Dr. Hammes.

17 DR. HAMMES: Richard Hammes.

18 I see three issues relative to the safety.  
19 First and overriding in my mind is the comparison with  
20 contrast. If we look at what's out there, this is so  
21 much safer that there is no comparison.

22 The second point though is we are looking  
23 at data, and this is a tracer and we need to remember  
24 that so that it's at subpharmacologic levels by  
25 definition, but there is data that shows platelet

1 inhibition at 30 times the dose, and we don't really  
2 know at what dose that starts, and I think that's  
3 something that needs to be followed up on a close  
4 market basis at the least.

5 And then the third issue is the  
6 immunogenicity, I guess, and the potential for  
7 multiple dosing in a sense, and an appropriate  
8 warning, you know, if it is approved to that effect,  
9 and further follow-up studies, I think, are warranted.

10 DR. KONSTAM: Marv Konstam.

11 You know, I hear you, and you know, I just  
12 want to ask. I mean, it is a tracer, but it's a  
13 peptide tracer, and it's an RGD peptide, and I just  
14 would ask: I mean, are we satisfied that it is in  
15 such low concentrations that, you know, we're clear  
16 about its immunogenicity and any other adverse effects  
17 that it might have?

18 I don't know. I mean, I'm uncomfortable  
19 about it, you know, given Dr. Zolman's comments. I'm  
20 willing to be convinced that there's a reason to feel  
21 safe. I'm just not sure. I'm not willing to go on  
22 record saying, yes, I'm convinced it's safe.

23 CHAIRPERSON RAMSEY: Could you please  
24 state your name?

25 DR. TALARICO: Talarico.

1           Some other RGD binders have been -- and we  
2           don't know anything about this product at all. So  
3           that should be looked for, is another safety issue  
4           that should be seen, looked for in a larger number of  
5           patients.

6           Generally, probably it's not much of a  
7           problem. It's a very small molecule, and in the  
8           patients, they didn't find any occupiers (phonetic).  
9           So it's likely it's going to be a big problem, but  
10          other events will have to be in doubt.

11          CHAIRPERSON RAMSEY: Dr. Hammes.

12          DR. HAMMES: Richard Hammes again.

13          To address your concerns, the other thing  
14          I look at is its very fast elimination. Given that  
15          fast renal clearance, I think if you're going to see  
16          a reaction in all likelihood it would be when its  
17          concentration is high in the first two or three hours,  
18          and we're looking at 700 patients in that time frame.  
19          I feel comfortable with that.

20          CHAIRPERSON RAMSEY: Dr. Ponto.

21          DR. PONTO: I would like to follow up  
22          Dick's comment there.

23          The half-life is 1.9 hours. Even the 169  
24          patients were basically studied at 12 half-lives. So  
25          we're looking at the time where the drug is

1 essentially eliminated from the body altogether, and  
2 they're not seeing anything substantial.

3 And as we said before, the alternative is  
4 iodinated contrast, and so we're talking about drugs  
5 that are given in much higher quantities, physical  
6 quantities, as well as a much worse side effect  
7 profile.

8 CHAIRPERSON RAMSEY: Dr. Jahnke.

9 DR. JAHNKE: Just a small disagreement.  
10 I think the alternative we're realistically looking at  
11 is ultrasound, which is real safe.

12 CHAIRPERSON RAMSEY: Good point.

13 All right. Let's move to Section 5, also  
14 known as Section 6. (a) Do you recommend AcuTect as  
15 approvable? This, as I understand it, doesn't mean  
16 approved, but could be approvable in the future, for  
17 the scintigraphic imaging of acute venous thrombosis.

18 DR. LOVE: Right, and I think just  
19 clarifications. Just thinking a we're moving some of  
20 the questions in order, but perhaps think about the  
21 issue of one study, two study as you think about this  
22 because in a way, the answers to whatever this is,  
23 3(c), have an impact on this part of the question and  
24 whether it's one or two studies.

25 CHAIRPERSON RAMSEY: Did everybody hear

1 that?

2 DR. D'AGOSTINO: Excuse me?

3 CHAIRPERSON RAMSEY: Yes.

4 DR. D'AGOSTINO: Does that mean that we  
5 would have to have two positive studies before we  
6 could say yes to this?

7 DR. LOVE: Well, we would listen to your  
8 comments and recommendations. As I said, there are  
9 circumstances where we have taken one study, but we  
10 would need to understand the reasons why and in this  
11 situation why is it an exception.

12 CHAIRPERSON RAMSEY: Shall be vote?

13 All in favor of recommending AcuTect as  
14 approved for --

15 DR. KONSTAM: I'm sorry to interrupt. I  
16 just wonder if now it wouldn't be worthwhile going  
17 back and voting about the individual trials because I  
18 think in order to keep internal consistency for  
19 ourselves, I mean if we're going to vote that it's  
20 approvable, then I think under ordinary standards we'd  
21 have to be voting that we have two positive pivotal  
22 trials, and so maybe that would be an appropriate  
23 starting point to figuring out whether it's approvable  
24 or not.

25 CHAIRPERSON RAMSEY: Committee agree with

1 that?

2 PARTICIPANTS: Yes.

3 CHAIRPERSON RAMSEY: All right. Let's  
4 back up to 3(c), numbers one and two. Is there  
5 someone on the Committee who would like to point out  
6 the key points of why one would or wouldn't accept  
7 280-32A and the same for 280-32B?

8 Dr. Links.

9 DR. LINKS: I'm going to be bold. I'm  
10 going to take Ralph's advice and try to get around all  
11 of these issues of whether you even have to use the  
12 Hamilton read for both and propose that we accept both  
13 studies, the first with the original read and the  
14 second with the Hamilton read.

15 So A with the original read and B with the  
16 Hamilton read, the justification for the substitution  
17 on B being the aberrant initial venography results.

18 CHAIRPERSON RAMSEY: Keeping in mind that  
19 venography is four carat and something else might be  
20 14 carat, not that all of us who have done venograms  
21 want to hear that, but there obviously are  
22 deficiencies with the technique. Am I out of line  
23 with saying that?

24 Any other comments?

25 DR. KONSTAM: Yeah, I guess I'll take the

1 other extreme, and you know, I just want to make clear  
2 that I really empathize with the problem that the  
3 sponsor is facing, which is that there is no adequate  
4 gold standard for acute venous thrombus. So that's  
5 the starting point, and that's a problem.

6 But I still come back to saying: okay.  
7 What do we learn from the data? And I don't really  
8 consider either study pivotal in the sense that it  
9 makes clear to me or to the clinician that we have an  
10 effective agent for detecting acute venous thrombus.

11 And I say it, and I guess the strongest --  
12 I mean, I guess I'll come down on Study A, which is,  
13 I think, technically a positive study based on its  
14 hypothesis, but I don't believe that it's an  
15 acceptable clinical finding to help me out clinically,  
16 and that's because I don't learn anything by knowing  
17 that AcuTect is at least 60 percent in conformity with  
18 the venogram. I just don't learn anything from that.

19 Now, I understand the problem. So then  
20 what do you do? And I have some suggestions for what  
21 to do. You know, I think, frankly -- I mean, we'll  
22 get to it -- I mean, I think Dr. Ginsberg pointed to  
23 what we should do because he feels the data are  
24 supportive of going forward and doing some kind of a  
25 real prospective clinical trial with some outcomes.

1 All I'm saying is I think that if we want  
2 to approve the -- if we think that there is something  
3 to approve here, I don't see it in these trials. I  
4 don't see how the trials help me say, yes, I should  
5 approve it for diagnosis.

6 DR. D'AGOSTINO: Can I comment?

7 CHAIRPERSON RAMSEY: Dr. D'Agostino.

8 DR. D'AGOSTINO: I also want to follow  
9 D'Agostino's advice --

10 (Laughter.)

11 DR. D'AGOSTINO: -- and come up with a  
12 slightly different conclusion.

13 I do agree very much with what was just  
14 said, but I also would say that in the first study  
15 they put together a study with a particular set of  
16 particular criteria, and that the 60 percent -- and  
17 they designed it and implemented it, and it turned out  
18 to be positive.

19 I think from that trial -- I think going  
20 into the second, which they were running  
21 simultaneously -- I think that it's unfortunate the  
22 way it turned out, but once you start going with the  
23 post hoc, I think you can no longer fall back on the  
24 interpretation of what you have in a strict fashion.

25 So I would say the second study didn't

1 make it, and I would say let the first study stand as  
2 a positive study, and from it learn the types of  
3 things you're saying, that it didn't really  
4 necessarily address the right question. Go on to  
5 design another study that, in fact, has a better  
6 endpoint, has a better training period, uses the  
7 Hamilton or what have you for the gold standard.

8 But I think that there is merit in the  
9 first study, and I think even though it may not be the  
10 ideal study, I think there is merit to call it a  
11 positive study, as long as there's a second study  
12 which then can be informed by it and designed and  
13 implemented correctly.

14 DR. AMENDOLA: Dr. Amendola.

15 I would really like to make a point here  
16 because I don't like for the entire panel to  
17 understand that right now what is now in clinical  
18 practice is nothing because I'm a practicing  
19 radiologist. I do ultrasound for DVTs, and really we  
20 study the calf down to the knees, and the calf is not  
21 really studied.

22 And let me tell you that we don't do  
23 venography, contrast venography. It's not really in  
24 standard practice. It's really the exception to the  
25 rule that we do contrast venography, and in fact, we

1 are not really trained to read it.

2 But right now as we stand, what we do when  
3 the ultrasound study is negative, what we do is we  
4 repeat the ultrasound studies three to five days later  
5 in the expectation that if there was a thrombus in the  
6 calf, the thrombus has extended to the thigh.

7 So really I would put forward here that  
8 today we don't really study calf.

9 CHAIRPERSON RAMSEY: Can I take the  
10 prerogative of the chair to make a comment?

11 MR. MADOO: Sure.

12 CHAIRPERSON RAMSEY: I've been in these  
13 Committee meetings before where we approved various  
14 agents, and I hope you won't laugh at me, but as I sit  
15 here listening to the data, and I don't do a lot of  
16 venography, but where the studies aren't perfect, the  
17 agent isn't perfect, the results aren't perfect, no  
18 test is perfect, and yet here is something, and it is  
19 something and perhaps something which I think I heard  
20 is probably helpful in the diagnosis of acute  
21 thrombosis, and perhaps something in the face of a  
22 life threatening illness is better than nothing, with  
23 the recommendation that other studies be done to  
24 substantiate safety factors, efficacy, sensitivity,  
25 and specificity.

1 DR. D'AGOSTINO: But you can do that  
2 before or after approval. I mean --

3 CHAIRPERSON RAMSEY: Well, as I read these  
4 questions, we're not approving it now. Nothing that  
5 we vote on here is approving it, but we're  
6 recommending for approvability, and therefore, that it  
7 could be -- maybe Dr. Love could have better words for  
8 it -- and then with the recommendation to go forward  
9 with other tests and to relook at some of the data as  
10 has been recommended.

11 DR. CHOYKE: Okay. This is often an issue  
12 that's difficult to sort out when we were at this  
13 point. Part of this depends upon whether you think  
14 there's enough information to say that one or both of  
15 the studies or all of the studies, whatever, tell you  
16 that there's a definite answer, and the answer that  
17 you have so far from these studies is not apt to  
18 change if you do a new study.

19 So, for example, if you thought that there  
20 was enough information, but you needed more  
21 clarification before labeling could be developed and  
22 clarify how the product would be used, then you might  
23 say it's approvable pending completion of those other  
24 studies.

25 If you thought that another study might

1 change your decision, meaning if you have a Study A  
2 and Study B and you weren't sure how they were going  
3 to come out, if you thought a second study might not  
4 confirm your findings, if you thought that was a high  
5 likelihood, then you might recommended nonapproval  
6 because you don't really know what's going to happen  
7 in the long run.

8 So those are some other issues to deal  
9 with. I guess we sometimes will say a product is  
10 approvable when we know that both clinical studies  
11 perhaps are adequate and acceptable, and we're just  
12 trying to sort out chemistry issues or something else.  
13 So we can certainly do that.

14 But if there's a one study/two study  
15 issue, unless you're sure or unless we have been sure  
16 in the past, often we would maybe say it's not  
17 approvable unless it's just a point of clarification  
18 as was mentioned earlier, trying to clarify labeling.

19 CHAIRPERSON RAMSEY: Dr. Konstam.

20 DR. KONSTAM: You know, I guess I just  
21 want to debate this point. You know, I hear the  
22 panelists saying that, you know, we don't have  
23 anything right now and so let's go ahead. I mean, I  
24 guess, not to be glib, but I would say we could have  
25 done that before doing these two trials if we really

1 want to say that.

2 I think we could probably have a starting  
3 point by saying the only thing that really would  
4 matter here is if we had a test that influenced  
5 treatment in a rational way, in a way that we could  
6 anticipate that if you have a positive test and you  
7 follow Treatment A, the patient will do well. If you  
8 follow Treatment B, the patient will not do well, the  
9 treatment here, I guess, being anticoagulation.

10 I am very, very, very far away from  
11 drawing the conclusion from these data that we have  
12 that test. I just don't have it. You know, I  
13 think -- let me put it this way. I'm no closer to it.  
14 I can imagine this conclusion based on the preclinical  
15 data, and I must say that for myself the clinical  
16 trial data don't bring me any closer to it because we  
17 know that venography is imperfect, and now we have an  
18 agent that is at least, in the best analysis of these  
19 two studies, even with the Hamilton analysis in the  
20 second study, it's at least 60 percent in agreement  
21 with venography.

22 I am nowhere near taking that result and  
23 saying, "Now I know that these patients should be  
24 anticoagulated and that will save their life or reduce  
25 the incidence of pulmonary embolism." I'm lost.

1           And what I would suggest -- what I will be  
2           recommending to the sponsor here is that we send them  
3           back to do the study that Dr. Ginsberg, who I'm sorry  
4           to see has left because I was going to ask him more  
5           about what exactly he would do; is now take the data  
6           that we have and do a prospective clinical study,  
7           taking patients with a negative scan. I think we have  
8           enough wherewithal to do that, and then follow the  
9           patients for six months and watch something that is  
10          important predefined clinical outcomes.

11                   And then if we found that, then we'd have  
12          something really important, and we would have done, I  
13          think, the entire medical community and their patients  
14          a service. I don't think we've done that at this  
15          point.

16                   CHAIRPERSON RAMSEY: Dr. Links.

17                   DR. LINKS: It seems to me that whether or  
18          not what you're saying is the way to go at least in  
19          part depends on the context in which this agent would  
20          hit the market. If the context is as a replacement  
21          for venography, it seems to me the type of study you  
22          would do is very different, more along the lines of  
23          what was done, than if the context in which it hits  
24          the market is that you assume that venography will be  
25          done at least a fraction of the time and this in some

1 way should augment the information provided by  
2 venography rather than replace it.

3 I personally don't have any problem  
4 couching this in the context of a replacement for  
5 venography because then the present study design is,  
6 in fact, an appropriate study design. The criterion  
7 of a 60 percent agreement may not be the right  
8 threshold, but if all you're going to do is say it's  
9 a replacement, then all you have to do is show that it  
10 agrees.

11 DR. KONSTAM: Well, I would counter by  
12 saying, first of all, it is only 60 percent, okay, and  
13 we've also heard repeatedly that nobody is going  
14 venography anymore. So why do we feel it's an  
15 acceptable criterion for provability to say that  
16 something has at least a 60 percent agreement with  
17 venography?

18 I just don't get it. I don't see it at  
19 all.

20 DR. JAHNKE: Dr. Jahnke.

21 But that was the FDA's recommendation, I  
22 believe.

23 DR. KONSTAM: We don't need to live with  
24 that.

25 DR. JAHNKE: Right. I know.

1 DR. KONSTAM: We understand that, and  
2 that's unfortunate, but it's not our business.

3 DR. JAHNKE: -- was backed into that, and  
4 there's something we have not talked about much, and  
5 it's clear we haven't talked about it much. We keep  
6 saying whether we should agree with the blinded read  
7 or the Hamilton setting, you know. The institutional  
8 read did agree with the Hamilton study also, which is  
9 the basis of the -- yes, it did. The institutional  
10 read agreed with the Hamilton study, and that's what  
11 the basis of the clinical treatment was in this  
12 series.

13 CHAIRPERSON RAMSEY: Right, because they  
14 had clinical data. I'm not even sure what order.  
15 We'll just go around the table.

16 Go ahead, please.

17 DR. AMENDOLA: I was kind of surprised of  
18 that fact, how the institutional read was much better,  
19 and I was wondering one of the reasons there was such  
20 an improvement was because the data from the  
21 ultrasound studies were taken into account.

22 CHAIRPERSON RAMSEY: Correct. Other data  
23 was taken into account.

24 DR. AMENDOLA: Because I don't believe  
25 that by notice of the clinical history that would

1 explain the improvement in the results.

2 CHAIRPERSON RAMSEY: Dr. Hammes.

3 DR. HAMMES: I'm real uncomfortable with  
4 the 60 percent level. You flip a coin and do just  
5 about as good obviously. The question is: where is  
6 this coming from? And it appears it's coming from the  
7 venography rather than the apcitide.

8 And if you look at all the other  
9 supporting studies, the institutional reads, the  
10 multiple human use, they all support its value, and I  
11 think we need to keep that in the back of our mind.

12 If I'm a patient with suspected DVT right  
13 now, give me a Doppler or give me this study and if  
14 they're both negative, don't give me therapy and let  
15 me go home.

16 DR. KONSTAM: What are the data that  
17 support what you just said? What data are your  
18 drawing upon to conclude that?

19 DR. HAMMES: The data that -- first off,  
20 venography I don't think would be a viable option for  
21 me given the inconsistencies we've seen and the  
22 morbidity.

23 Secondly, Doppler is very good if you know  
24 where the thrombus is to begin with, you know. You've  
25 got a sore spot in your leg, and you can aim the

1 Doppler at it, and you can find it. In the absence of  
2 those localizing symptoms, Doppler doesn't find it.

3 We saw data that said that the apcitide  
4 was quite sensitive, especially in the acute setting.  
5 Hence, a negative apcitide study and a negative  
6 Doppler study and seven percent morbidity from therapy  
7 of anticoagulation, I think we add something  
8 significant to the medical practice by making this  
9 tool available and at least screen out that portion of  
10 the patient population and with some significant  
11 benefit, also keeping in mind the relative safety of  
12 it.

13 CHAIRPERSON RAMSEY: Dr. Choyke.

14 DR. CHOYKE: I'd just like to make two  
15 points. One is that it's quite possible and quite  
16 likely, given the magnitude of venous thrombosis as a  
17 problem in this country that if this agent was  
18 approved, that outcome studies such as the one you  
19 would envision would be readily funded. It's of such  
20 magnitude that I think it would happen.

21 And I don't think -- I mean, I haven't  
22 been involved with that many of these sessions, but I  
23 think the holding the sponsor to the standard of an  
24 outcome study is atypical. It's not typically what's  
25 required.

1           What's required is to show some degree of  
2 efficacy for the agent, which I think if you believe  
3 the Hamilton read, you can show some degree of  
4 efficacy. It may not be the perfect drug. It likely  
5 isn't the perfect drug, but I believe that outcome  
6 study that really should be done will be done in our  
7 current, you know, situation.

8           DR. KONSTAM:     Well, I guess we can  
9 recommend to the FDA that they require that the study  
10 be done either before approval or after approval; is  
11 that right?

12           DR. LOVE:     Yes, that's correct.

13           CHAIRPERSON RAMSEY:    Dr. D'Agostino.

14           DR. D'AGOSTINO:    We use vocabulary in  
15 different ways. When I sometimes use the term  
16 "outcome study," it's a completely uncontrolled study  
17 that I'm just looking at practice.

18           I think that what I'm talking about, a  
19 clinical trial which may have a longer follow-up, but  
20 not in a typical effectiveness outcome study fashion.  
21 I don't know. Maybe you're referring to outcome study  
22 in a different fashion than I am.

23           DR. AMENDOLA:     I'd also like to make  
24 clear, and I have an article here by Dr. Cronan, which  
25 is one of the experts in ultrasound of the DVTs. Let

1 me read it to you.

2 "If clot is isolated to calf veins, it is  
3 recognized that upward propagation, popliteal vein  
4 involvement occurs in approximately 20 percent of  
5 cases. Propagation of clot can be . . . if ultrasound  
6 studies are performed at three to five days  
7 intervals."

8 The reason for this is because with  
9 ultrasound we don't study the calf. Most institutions  
10 do not study the calf. So there is an area that we  
11 have not -- and we are certainly not doing contrast  
12 venography for that episode.

13 CHAIRPERSON RAMSEY: Dr. Ponto.

14 DR. PONTO: As Dr. Ramsey referred to  
15 earlier, I've been involved in some of these decisions  
16 where the question is do we want to give the  
17 clinicians a new tool that they don't have already,  
18 and it's quite obvious that this area needs a new  
19 tool. The question is: is this the right one or not?

20 And that's what I'm grappling with, and do  
21 these studies convince us that this is the right tool?

22 If the differences we saw in the agreement  
23 rates could be attributed to the fact that the  
24 apcitide was telling us something that the venography  
25 was not, then I would be more comfortable with giving

1 people this tool to work with, but because they didn't  
2 give us any outcome data, did not look to see who had  
3 a pulmonary embolism and who did not, I don't know if  
4 those differences are just because we cannot read the  
5 studies adequately or because it is a better tool.

6 And so I'm feeling sort of like Mark is  
7 over here, that there's the need for another study  
8 that looks at outcome, that looks at a different  
9 predictive variable, maybe ultrasound, maybe not  
10 venography, but something that says that the people  
11 with a positive study have a worse prognosis than the  
12 people with a negative study.

13 CHAIRPERSON RAMSEY: But there are also  
14 clinical implications beyond just positive and  
15 negative study.

16 Dr. D'Agostino.

17 DR. D'AGOSTINO: Not to be a legalist, but  
18 we're all talking or those who are talking about it a  
19 study are talking about one study. The FDA wants two  
20 studies, and this is my logic of saying Study A looks  
21 all right as long as it informs us about a very good,  
22 new study.

23 CHAIRPERSON RAMSEY: Dr. Love.

24 DR. LOVE: Yes, the studies do not have to  
25 be identical as long as they corroborate in some

1 manner or another.

2 CHAIRPERSON RAMSEY: Dr. Rohde.

3 DR. ROHDE: Yes. Charles Rohde from Johns  
4 Hopkins.

5 I'd like to hopefully clarify an issue  
6 about the 60 percent. The 60 percent is not the best  
7 estimate of agreement of these two methods. It is the  
8 lowest value which is supported by the data. The  
9 actual numbers, estimates from the data, are in the 70  
10 percent range.

11 And if you put an upper confidence limit  
12 on it, that would go very close to 80 percent. So the  
13 suggestion that we're talking about something that's  
14 about like flipping a coin is a little misguided.

15 And the sponsor was told that this was the  
16 criteria, and that was the criteria. It may be that  
17 this study should have been run in some different way.  
18 What it sounds like to me, everyone is saying that  
19 there should have been a different outcome looked at  
20 and so forth, but what we have is something like 70  
21 percent agreement.

22 Now, I'm not convinced that we cannot get  
23 more information from this data than we have. For  
24 example, we do have the original records, in which  
25 both readings were positive, in which both were

1 negative, and some were positive and the other was  
2 negative.

3 We also have patient characteristics for  
4 these data. We have the ability now to put in an  
5 effect for differences between readers, and it would  
6 not surprise me that a really careful analysis would  
7 demonstrate that these two methods are absolutely  
8 equivalent.

9 That hasn't been done, but it probably  
10 could be done with the right people and the right  
11 help, and it could be done probably very quickly.

12 So it strikes me that there's just about  
13 as much doubt in my mind about the positive  
14 implications as there are about the negative  
15 implications. It's just, you know, we've gotten  
16 railroaded into looking at one specific issue, and I'm  
17 not sure if it's exactly the right one.

18 CHAIRPERSON RAMSEY: I'd like to bring us  
19 back in order to move forward here, if we could vote.  
20 I'm not sure that we can or maybe it's inappropriate,  
21 but (c)(1), do you recommend accepting Study 280-32A  
22 as one of the two pivotal studies to demonstrate the  
23 efficacy of AcuTect for scintigraphic imaging to  
24 detect acute venous thrombosis, yes or no?

25 So all those who would accept it, please

1 raise your hand.

2 (Show of hands.)

3 MR. MADOO: It looks like we have ten out  
4 of 12. Could those who were not accepting raise their  
5 hands so we can verify that?

6 (No response.)

7 MR. MADOO: Are any abstaining?

8 MR. MADOO: We have one extension. It  
9 looks like we're missing a vote.

10 DR. KONSTAM: I voted no.

11 MR. MADOO: You voted no? Okay.

12 CHAIRPERSON RAMSEY: I'll vote to accept.

13 MR. MADOO: Okay. Dr. Ramsey will vote to  
14 accept. So we have 11 accepting and one, Dr. Marvin  
15 Konstam, no, not accepting.

16 CHAIRPERSON RAMSEY: All right. (c)(2)  
17 Do you recommend accepting Study 280-32B as one of the  
18 two pivotal studies to demonstrate the efficacy of  
19 AcuTect for scintigraphic imaging to detect acute  
20 venous thrombosis? Again, yes and no.

21 All those who would accept it, say yes.  
22 Raise your hand, yes.

23 (Show of hands.)

24 MR. MADOO: It looks like seven.

25 CHAIRPERSON RAMSEY: All those opposed

1 raise your hand.

2 (Show of hands.)

3 MR. MADOO: Five opposed.

4 CHAIRPERSON RAMSEY: All those abstaining.

5 That's 12. Sorry. I'll get out my checkbook here.

6 DR. LOVE: Excuse me. Question. Just for  
7 sake of numbers, you were voting on the first  
8 question, but not the second?

9 MR. MADOO: No, no.

10 CHAIRPERSON RAMSEY: I voted yes.

11 DR. LOVE: I'm sorry. The second one then  
12 is?

13 CHAIRPERSON RAMSEY: Seven to five.

14 DR. LOVE: Seven to five. Thank you.

15 CHAIRPERSON RAMSEY: All right. Let's go  
16 back to the last set of questions then. Do you  
17 recommend AcuTect as approvable for the scintigraphic  
18 imaging of acute venous thrombosis? And this, again,  
19 is not for approval. It's just approvable.

20 I think once we voted -- I guess you're  
21 right. It does have to be -- you're right. You're  
22 right. You're right, but sometimes it's much more  
23 overwhelming than others. Sometimes they don't listen  
24 to us.

25 DR. PONTO: Point of clarification. This

1 vote is based on the current status of the data,  
2 correct, not on any kind of reanalysis?

3 CHAIRPERSON RAMSEY: Right. That will  
4 come up in the next -- I think in (c). We'll make  
5 recommendations.

6 Are we right, Dr. Love?

7 DR. LOVE: Yes.

8 CHAIRPERSON RAMSEY: So okay. Yes is you  
9 say yes to the approvability. No is you do not agree  
10 with approvability.

11 So all those who are in favor of  
12 approvability for the scintigraphic imaging for acute  
13 venous thrombosis say yes; raise your hand yes.

14 (Show of hands.)

15 MR. MADOO: Seven.

16 CHAIRPERSON RAMSEY: All those no?

17 (Show of hands.)

18 MR. MADOO: Four no.

19 CHAIRPERSON RAMSEY: Abstaining?

20 MR. MADOO: It looks like we're missing a  
21 person.

22 CHAIRPERSON RAMSEY: One abstention.

23 MR. MADOO: One abstention.

24 CHAIRPERSON RAMSEY: Okay. Back to  
25 discussion. Is there any other indication that you

1 recommend?

2 That's kind of a curve ball here, right.  
3 Let's skip that for now.

4 If you do not recommend AcuTect, but let's  
5 just leave that as open, for open discussion again, as  
6 approvable, are there other studies or trial designs  
7 that you would recommend to be completed before  
8 approval?

9 We've heard some discussion of that  
10 already. Looking at the data again, seeing if we  
11 could get more out of it.

12 Dr. Kasper.

13 DR. KASPER: Well, other than looking at  
14 the data again, perhaps given the discussion around  
15 the table that venograms are not done very much  
16 anymore except in a few places such as Hamilton,  
17 perhaps the FDA should reconsider its position that  
18 the comparison ought to be made with sonography,  
19 certainly for above the knee.

20 CHAIRPERSON RAMSEY: Dr. Love is that  
21 okay?

22 Any other comments? Dr. August.

23 DR. AUGUST: I think we have a problem  
24 that is worth going back to, and that is that one of  
25 the main issues with the failure of venography to be

1 a true gold standard is that the image will be  
2 positive if there is an old, organized thrombus that's  
3 just hanging in the vein, and the same is true for  
4 ultrasound, so far as I can tell.

5 So given that the AcuTect is going to  
6 detect acute emerging thrombi and not the old ones,  
7 there's always going to be a real problem with  
8 discrepancy between presumably a higher number of  
9 images that are going to be positive by venography or  
10 ultrasonography and a lower number presumably that are  
11 going to be positive using AcuTect.

12 And I think if we don't recommend that a  
13 study be designed to take that into consideration and  
14 somehow get around it, then there will be  
15 dissatisfaction with the extent of agreement or  
16 whatever with every study that this Committee is asked  
17 to critique.

18 CHAIRPERSON RAMSEY: Dr. Ponto.

19 DR. PONTO: I'd like to follow up on that  
20 and recommend that outcomes be involved in any study  
21 in the future and reiterate what Dr. Kasper said, that  
22 we need to use the current technology that would be  
23 used in these patients, that being ultrasound.

24 I would also like to recommend that the  
25 company institute the same type of a mechanism that

1 has been done with some of the more recent drugs that  
2 we've approved, that they have very rigorous training  
3 for their readers so that we would not have the  
4 disagreement that we saw with the readers that we saw  
5 in this particular study, both in a study context, as  
6 well as possibly in its clinical utility.

7 CHAIRPERSON RAMSEY: Other comments?

8 Dr. Love? Oh.

9 DR. TALARICO: This is Lilia Talarico.

10 I'd like to make a comment on the  
11 differentiation between diagnosis of DVT or clinical,  
12 clinical DVT versus DVT that's going to be picked up  
13 for thromboprophylaxis, for example, in surgery,  
14 abdominal surgery, et cetera.

15 When you're dealing with  
16 thromboprophylaxis, noninvasive tests are very poor,  
17 and venography must still play a role for diagnosis of  
18 DVT in thromboprophylaxis. So venography is not out.

19 CHAIRPERSON RAMSEY: We're not throwing it  
20 out the window, but nobody wants to do it or have it.

21 DR. KONSTAM: No, I -- may I speak?

22 CHAIRPERSON RAMSEY: Yes.

23 DR. KONSTAM: Marv Konstam.

24 I guess I've said this a couple of times,  
25 but I guess this is a good place to say it again. Of

1 course, I voted for not approvability. So I'd like to  
2 see this done before approval, but if we're going to  
3 vote approvability, then I'd like to suggest that the  
4 FDA request a study, a Phase IV study.

5 And, you know, here's what I think. I  
6 mean, I think let's think of the implications of what  
7 we've approved. I mean, we've approved an agent for  
8 detection of acute venous thrombus with the  
9 presumption that that has an implication on therapy,  
10 and we don't know exactly how it's going to be used in  
11 the field. We really don't.

12 I mean, we've heard some comments about  
13 how people think they might use it or would recommend  
14 using it, but I'm not sure that's going to make its  
15 way into the labeling.

16 I think what's going to happen is that the  
17 agent is going to get out into the field, and it's  
18 going to be used variably. Now, what I'd like to see  
19 is to know what happens to a patient who has a  
20 negative study and is sent home, and I think that this  
21 is a critical, important question because this is what  
22 is going to happen in the community, and I think that  
23 there's an obligation here to learn what happens when  
24 that happens, and I think it's also a great  
25 opportunity.

1           So I would design the study accordingly.  
2           The specificity to my reading is clearly fairly low.  
3           So the advantage is that a negative study, sensitivity  
4           is a little higher. Take patients who have a negative  
5           study, send them out without treatment, and follow  
6           them prospectively, and then the details of that can  
7           be worked out in terms of the duration of follow-up  
8           and the outcomes that we want to follow.

9           But I would urge very strongly that the  
10          company be required to do such a study.

11          CHAIRPERSON RAMSEY: Thank you.

12          Dr. Hammes. Sorry.

13          DR. HAMMES: Yeah, Richard Hammes.

14          I concern with Dr. Ponto that we need some  
15          outcomes data as part of this inevitably. I would  
16          also suggest that in future studies -- and I'll have  
17          to defer to our radiology colleagues -- but it seems  
18          to me that if you could direct ultrasound with the  
19          nuclear study, ultrasound ought to be able to confirm  
20          the presence of absence of a clot, and that may be a  
21          viable approach to get a better gold standard at least  
22          in the positive results.

23          DR. AMENDOLA: Dr. Amendola.

24          I think that that is a very logical  
25          question, and I think that ultrasound should be used

1 as the comparison, not venography because venography,  
2 one, is not, as we heard before, it's not a gold  
3 standard, and, second, it's not used, but ultrasound  
4 is used every day.

5 CHAIRPERSON RAMSEY: Any other comments?

6 Yes.

7 DR. CHOYKE: I'd just like to point out  
8 that the company started with ultrasound, but it was  
9 recommended by the agency that they shift to contrast  
10 venography. So, you know --

11 CHAIRPERSON RAMSEY: Yes, we heard that  
12 earlier.

13 DR. CHOYKE: -- that's a little unfair.

14 CHAIRPERSON RAMSEY: They're responding to  
15 our request, right? Well, the FDA's request.

16 DR. LOVE: The change from ultrasound to  
17 contrast venography, yes, was after we talked with  
18 them about the issues of the calf and pelvis, and we  
19 were talking about you don't know prospectively where  
20 the patient is going to have the abnormality, and that  
21 was the rationale behind changing to the contrast  
22 venography.

23 The sponsor did do a reasonably large size  
24 study. I think it was 100-and some odd patients, 200,  
25 in that study. That study was completed from a safety

1 perspective and analysis, and some of that immuno --  
2 no, the immunogenicity data was not that one.

3 But at any rate, they did do a study, and  
4 there was some analysis done by Dr. Sobhan just to try  
5 to look to see whether there was any difference in the  
6 results just in terms of percentages of positive or  
7 negative with the ultrasound or the contrast  
8 venography, and there wasn't much difference.

9 These are all different data sets,  
10 different studies, but the results weren't appreciably  
11 different.

12 CHAIRPERSON RAMSEY: Dr. Links.

13 DR. LINKS: A radical comment. It seems  
14 to me that half of our discussion has been the result  
15 of not a poor study, but a poor study design relative  
16 to the indication, and I, for one, all through the day  
17 have been somewhat frustrated that in a sense the  
18 studies that we have before us are not the studies you  
19 would do to specifically address the proposed  
20 indication, but they sound like they were certainly  
21 the studies that ultimately the company and the FDA  
22 together decided were the studies to be done.

23 And I'm just wondering if we're the group  
24 that's supposed to grapple with recommendations after  
25 the fact, shouldn't we have a shot at grappling with

1 study design issues at least some of the time before  
2 the Phase II trials start.

3 DR. LOVE: Yes, you may, and we would  
4 certainly love if you would look at this. If there is  
5 a recommendation for a new protocol, we'd love to  
6 bring it back to the Committee.

7 DR. KONSTAM: Yeah, but you know, wouldn't  
8 it have been a loud statement to make that as a  
9 comment about the -- sorry, but you know, I agree. I  
10 agree with what you're saying, and I think that really  
11 that statement becomes loud if you say, "You know  
12 what? This data set doesn't really support  
13 approvability. This is the study," and forget what  
14 the FDA recommended to years ago or whatever it is.

15 But, you know, sorry to keep -- but I  
16 agree with you. I think it is appropriate for us to  
17 say what we think is good criteria for approving or  
18 not approving an agent like this.

19 CHAIRPERSON RAMSEY: Having been involved  
20 in a number of studies, you go into them thinking that  
21 this is the right thing to do, and then when you look  
22 back and say that really isn't what I wanted to do  
23 after all, but I think when you started you thought it  
24 was, and you went in with every good intent, and I  
25 think it's just after you get done that you realize

1 that it didn't give you the answer that you were  
2 actually looking for.

3 So I'm not absolutely positive it's poor  
4 design, although it might be.

5 But that being said, let's move on to (d),  
6 and I think we pretty well covered (d).

7 DR. LOVE: Right. Could I ask a question  
8 back on (c)? (c) says do you recommend that this is  
9 done before approval, and so what you've recommended  
10 is approvability. Do you -- on this study that you're  
11 talking about, or studies, whatever it might be, are  
12 you recommending that that's done before it is  
13 approved or after it is approved, meaning in Phase IV  
14 or beforehand?

15 CHAIRPERSON RAMSEY: I think we're going  
16 to have to vote on this one.

17 Do you recommend AcuTect as approvable?  
18 If you do -- oh, if you do not. Well, let's say if we  
19 do. If we do recommend, and we did, would you like  
20 other studies or trial designs to be completed before  
21 approval?

22 DR. AMENDOLA: I think we have to decide  
23 which studies.

24 CHAIRPERSON RAMSEY: And then which one.

25 DR. LOVE: Well, I don't necessarily --

1 I'm not really asking for which, but basically you've  
2 recommended some outcome studies, and I've heard  
3 different perspectives on whether or not you need to  
4 know that before labeling can be developed versus  
5 after, basically before you know how to use the  
6 product versus after you know how to use the product.  
7 So that's why I'm asking that question.

8 CHAIRPERSON RAMSEY: Oh, boy, that's a  
9 hard one because outcomes are sometimes ponderable,  
10 not always obtainable, and there were other things  
11 that I think the Committee asked, and that is to  
12 remassage the data that's available already and bring  
13 that forth to look at it again.

14 And Dr. August and then Dr. Links.

15 DR. AUGUST: Charles August.

16 I do think that they ought to respond to  
17 the issue of safety with longer -- with a longer time  
18 period of observation and larger numbers, and I think  
19 that's quite possible, and I think that it may well be  
20 that the immunogenicity issue could be settled by  
21 maybe another draw, a month, six weeks down the line.

22 CHAIRPERSON RAMSEY: Dr. Ponto -- no,  
23 somebody else. Oh, Dr. Links. I'm sorry.

24 DR. LINKS: Since the majority already  
25 voted for approvability, perhaps a way out of this

1 particular conundrum is to suggest that the outcomes  
2 trial, which I think all of us, including those who  
3 voted for approvability, would like to see be done as  
4 a Phase IV with the long term approval conditional on  
5 accomplishing that Phase IV trial within -- in other  
6 words, approval to be withdrawn if the Phase IV isn't  
7 accomplished within some time frame that the FDA sets.

8 DR. LOVE: There are some regulations that  
9 allow that. Normally they are very specific  
10 statements for accelerated approval that hasn't been  
11 accomplished thus far. So we can take that under  
12 advisement, but I don't know if there's a regulatory  
13 mechanism to complete get us out of that.

14 DR. D'AGOSTINO: Why don't we just  
15 reconsider what we did before and ask them to have  
16 this done before approvable? I mean, I think that the  
17 studies are very important, and we just don't have all  
18 of this information.

19 DR. LINKS: Question. How long would such  
20 a trial take?

21 DR. D'AGOSTINO: Let's let the company  
22 worry about it.

23 DR. LINKS: No, I'm asking a clinical  
24 question. How long is adequate follow-up?

25 DR. D'AGOSTINO: Oh, oh, oh, you're

1 talking about how long the outcome period.

2 DR. LINKS: Yeah, right.

3 DR. D'AGOSTINO: Some people say in six  
4 months. I don't know if that would be idea, but six  
5 months sounds reasonable.

6 DR. KONSTAM: I'd be satisfied with six  
7 months. I don't know what other people think. I mean  
8 if you -- if somebody came in with a questioned  
9 diagnosis of DVT and went home with no therapy, what  
10 would we consider a reasonable period of follow-up to  
11 know that we didn't do any harm? Six months to me  
12 seems pretty reasonable. Maybe less, maybe three  
13 months is reasonable. I don't know. Certainly no  
14 more than six months. I don't think we'd need --

15 DR. AMENDOLA: Probably three months.

16 DR. KONSTAM: Three months might be okay,  
17 somewhere in that range.

18 CHAIRPERSON RAMSEY: Any other comments?  
19 Dr. August.

20 DR. AUGUST: I think that the likelihood  
21 is good that if and when this is on the market it's  
22 going to be used repeatedly at least in a subset of  
23 patients who may have a chronic problem, and I'm  
24 curious to know whether my view is shared by the  
25 people who actually take care of these patients and

1 whether or not we shouldn't anticipate that issue with  
2 some suggestions for guidelines that might be given by  
3 the FDA to the company.

4 CHAIRPERSON RAMSEY: Dr. Love.

5 DR. LOVE: I guess I interpreted that as  
6 a question to the panel.

7 CHAIRPERSON RAMSEY: Well, I think someone  
8 recommended 600 patients for follow-up, and you said  
9 it could be done with less. So I think we could maybe  
10 defer to the FDA to decide on a number that would be  
11 necessary for safety.

12 DR. LOVE: Maybe I misunderstood your  
13 point.

14 DR. AUGUST: My question was quite a  
15 different one, and that is that even with the safety  
16 record that it now enjoys, I think the temptation will  
17 be great in a subset of patients who have chronic  
18 problems to use this technique over and over again,  
19 and yet everything that we've heard about today has  
20 been the results of a single study.

21 And my question really is: should we  
22 anticipate? I would like some guidance from the  
23 physicians, the clinicians who take care of these  
24 patients as to whether my surmise is correct.

25 And then if it is, are there some

1 anticipatory suggestions or guidelines that the FDA  
2 could make in that regard, the simplest being, I  
3 suppose, to emphasize in the labeling that this study  
4 and the safety and efficacy data that we have pertain  
5 only to patients who were studied once, and we can't  
6 guarantee, for example, that if they were injected  
7 repeatedly with this polypeptide that there would not  
8 be an immune reaction and there might not be  
9 anaphylaxis on the second or third or whatever  
10 exposure.

11 And you could probably come up with some  
12 other things as well.

13 DR. LOVE: Okay. Yes, certainly there is  
14 a history of putting such warnings or comments in the  
15 labeling if there's a limited safety database.

16 I guess what I also heard you asking  
17 though is are there some recommendations or guidelines  
18 for repeat dose studies, and that's where I thought  
19 you were asking the other panelists if there were some  
20 things that you wanted to recommend on how that might  
21 be studied; is that correct? Is that what you're  
22 asking?

23 DR. AUGUST: Well, what I asked was if  
24 there were clinicians who would comment on the  
25 likelihood that there would be patients who would be

1 treated over and over again, and then if there were,  
2 then should we produce or should we recommend to you  
3 that you create some guidelines for that repeated  
4 usage so that perhaps people can be aware that the  
5 data that we have and on which we recommended  
6 approvability was limited.

7 DR. AMENDOLA: So the issue is the repeat  
8 doses, and as far as we can determine there is no  
9 safety issue, no knowledge about the safety of that.

10 DR. LOVE: Right, no knowledge.

11 DR. AMENDOLA: So now we have this three  
12 or five days at least.

13 CHAIRPERSON RAMSEY: Dr. Konstam.

14 DR. KONSTAM: You know, I'd just like to  
15 say, you know, I attend on the cardiology wards, and  
16 there are patients that are going to come in with  
17 questions of deep venous thrombosis, and after this  
18 drug is approved, based on the data set that we have  
19 now, I am not going to know how to use it.

20 I've heard many suggestions about how to  
21 use it. Some of them seem cogent, but they're not  
22 really supported by the data set. I think the  
23 suggestion was that based on the level of sensitivity  
24 that we see in a subset of patients who presented with  
25 symptoms within the last three days, we might be safe

1 accepting that as a solitary test and sending the  
2 patient out.

3 I think that the data that I see show that  
4 that's a reasonable hypothesis, but I'm not totally  
5 convinced about that.

6 And I also don't know what to do about a  
7 positive test. I'm not sure whether we see anything  
8 in the data set that tells us how to handle a positive  
9 test. Is a positive test a trigger to do a venogram,  
10 which isn't commonly done? Is it a trigger to do an  
11 ultrasound?

12 Again, I mean, we could come up with  
13 recommendations, but I guess we need to. Someone  
14 needs to come up with recommendations about how to  
15 handle these different contingencies.

16 I for one do not see guidance in the data  
17 set about how to deal with these questions.

18 CHAIRPERSON RAMSEY: Dr. Jahnke.

19 DR. JAHNKE: Therefore, you agree with the  
20 FDA that this agent is not approvable for the  
21 detection of thrombosis, I guess. I mean, that was  
22 Dr. Jones' conclusion. That was mine also.

23 DR. KONSTAM: Yeah.

24 DR. JAHNKE: And my question, and it may  
25 not be proper to answer this, but you, of course,

1 don't have to agree with the opinion of the Advisory  
2 Committee in taking it into consideration, I assume.

3 DR. LOVE: Yes. Just a process note.  
4 Basically when the preliminary reviewers make a  
5 recommendation before something has come to the  
6 committee, that's basically the review team  
7 recommendation. After we listen and consider all of  
8 the points that you've recommended, then the final  
9 action is taken.

10 So we will very strongly consider  
11 everything that's been said here. There are times  
12 that the agency has agreed with -- this across the  
13 board. We're not just talking about this Committee --  
14 there are times when the agency agrees with a  
15 recommendation. There are times when it does not. I  
16 think it's appropriate that if we do not follow your  
17 recommendations, that we would communicate with you  
18 about what the issues were and why if we are not.

19 What I'm hearing is a lot of different  
20 sets of perspectives from the Committee on all of  
21 these issues.

22 CHAIRPERSON RAMSEY: I'd like to also go  
23 to 5(b). Are there any other indications that you  
24 would recommend?

25 I'm not sure that's appropriate. Dr.

1 Links said no. I'm not sure if that's appropriate  
2 under our topics for today, but it's there so I wanted  
3 to address it.

4 Dr. Jahnke.

5 DR. JAHNKE: Going back to something Dr.  
6 Love said earlier that we somewhat skipped around,  
7 addressing the issue of straining versus definitive  
8 evaluation. I don't think we have addressed that  
9 adequately, have we?

10 CHAIRPERSON RAMSEY: I don't think we --

11 DR. JAHNKE: Some of it goes to what Dr.  
12 Konstam said.

13 CHAIRPERSON RAMSEY: It's been mentioned.

14 DR. JAHNKE: I mean, should this be used  
15 as a screening exam if you have a low or moderate  
16 level of confidence?

17 CHAIRPERSON RAMSEY: Low prob.

18 DR. JAHNKE: Versus a definitive  
19 examination if you have a high level of suspicion.

20 CHAIRPERSON RAMSEY: I think that  
21 dovetails in with saying that we need more studies,  
22 that we need to look at it more. So at the present it  
23 would probably be a screening, but I guess I can't  
24 actually answer that.

25 Any other comments from any other panel

1 members?

2 (No response.)

3 CHAIRPERSON RAMSEY: Mr. Madoo, is there  
4 anything else?

5 MR. MADOO: No, I guess we're done, right,  
6 Dr. Love?

7 CHAIRPERSON RAMSEY: I was just going to  
8 ask Dr. Love if there was anything else she wanted us  
9 to --

10 DR. LOVE: I think you're certainly  
11 covered. I'd like to take a moment just to thank you  
12 very much for your detailed consideration of this.  
13 These are a lot of important issues. Certainly we've  
14 dealt with issues that surround receptors in general.  
15 Some of these issues are things that the Committee  
16 discussed with the guidance document, looking at  
17 physiologic or biochemical issues, and here you have  
18 an anatomic standard of truth.

19 So these are issues that are going to be  
20 important in the long run.

21 You've also dealt with issues about  
22 agreement studies, and that's going to be a  
23 prospectively active issue that we'll have to continue  
24 to address.

25 But I thank you very much for your

1 comment.

2 CHAIRPERSON RAMSEY: Thank you.

3 I'd like to also thank all of the panel  
4 members for coming. I think this has been one of the  
5 more interesting panels where we really dug at some  
6 issues. I want to thank all of you for taking the  
7 time to come here, and thank everybody in the audience  
8 and the presenters, as well.

9 (Whereupon, at 3:44 p.m., the meeting was  
10 concluded.)

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