

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**ADVISORY COMMITTEE: MEDICAL IMAGING DRUGS**  
**ADVISORY COMMITTEE**

**DATE OF MEETING: 02/09/98**

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**SLIDES**

# AcuTect™

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Kit for the Preparation of Technetium  
Tc 99m Apcitide

Medical Imaging Drugs  
Advisory Committee Meeting

February 9, 1998



# AcuTect™

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## Proposed Indication:

AcuTect is indicated for the  
scintigraphic imaging of acute venous  
thrombosis



# AcuTect™

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Clinical Development

1992-1997

NDA Submitted

August 19, 1997

Priority Review Classification



# AcuTect™

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## Diatide Consultants

Michael A. Bettman, M.D.

*Chief, Cardiovascular and Interventional  
Radiology*  
Dartmouth-Hitchcock Medical Center

Jeffrey Ginsberg, M.D.

*Director, Thromboembolism Unit*  
Hamilton Health Science Corp.

Alexander Gottschalk, M.D.


*Professor of Radiology*  
Michigan State University

H. Dirk Sostman, M.D.

*Professor and Chairman of Radiology*  
New York Hospital/Cornell Medical Center

Raymond Taillefer, M.D.

*Chief of Nuclear Medicine and  
Clinical Investigator*  
Hopital Hotel Dieu De Montreal



# AcuTect™

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## Diatide Presenters

J. Kris Piper

Senior Director Regulatory Affairs

John Lister-James, Ph.D.

Senior Director Research & Development

Richard T. Dean, Ph.D.

CEO and Chief Scientific Officer



# AcuTect™

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## Presentation

**Introduction**

**J. Kris Piper**

**Discussion of the Clinical  
Problems Surrounding Diagnosis of DVT**

**H. Dirk Sostman, M.D.**

**Scientific Rationale for AcuTect**

**John Lister-James, Ph.D.**

**Clinical Study Overview**

**Richard T. Dean, Ph.D.**

**AcuTect Image Reading Criteria**

**John Lister-James, Ph.D.**

**Review of Efficacy Data**

**Richard T. Dean, Ph.D.  
Jeffrey Ginsberg, M.D.  
Alexander Gottschalk, M.D.**

**Review of Case Studies**

**Raymond Taillefer, M.D.**

**Conclusion**

**Michael Bettman, M.D.**





# AcuTect™

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- Receptor binding properties
- Detection of acute thrombosis
- Pivotal trial design and results
- Hamilton blind read
- Proof of Safety and Effectiveness



# AcuTect™

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## SCIENTIFIC BASIS

- Product need
- What is AcuTect™
- Why it should work
- How it works



# Product Need

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## Thrombosis

Thrombus Biochemistry  $\longleftrightarrow$  Disease State

**Acute vs Chronic**



# Thrombus Imaging

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## Radiolabeled Platelets

- Shown to be useful for acute venous thrombosis

**Indium-111 platelet scintigraphy for the diagnosis of acute venous thrombosis**

MICHAEL D. EZEKOWITZ, M.B., CH.B., PH.D., CHRISTOPHER F. POPE, M.B., CH.B.,  
H. DIRK SOSTMAN, M.D., EILEEN O. SMITH, B.S., MORTON GLICKMAN, M.D.,  
STANLEY RAPOPORT, M.B., CH.B., KENNETH W. SNIDERMAN, M.D.,  
GARY FRIEDLAENDER, M.D., RICHARD R. PELKER, M.D., PH.D.,  
FLETCHER B. TAYLOR, M.D., AND BARRY L. ZARET, M.D.

*Circulation 73, No. 4, 668-674, 1986.*

- Limitations
  - Inconvenient preparation
  - Blood clearance too long

# Thrombus Imaging

## I-125 Fibrinogen

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- FDA approved at one time
- Shown to be useful for acute venous thrombosis

**Replacement of Venography in Suspected Venous Thrombosis by Impedance Plethysmography and <sup>125</sup>I-Fibrinogen Leg Scanning**

**A Less Invasive Approach**

RUSSELL HULL, M.B., B.S.; JACK HIRSH, M.D.; DAVID L. SACKETT, M.D., M.Sc.; D. WAYNE TAYLOR, M.A.; CEDRIC CARTER, M.B., B.S.; ALEXANDER G.G. TURPIE, M.B., B.S.; ARIEL ZIELINSKY, M.D.; PETER POWERS, M.D.; and MICHAEL GENT, M.Sc.; Hamilton, Ontario, Canada

Annals of Internal Medicine. 1981;94:12-15

- Limitations
  - Removed from market / blood product
  - Slow clearance required 24 hr scanning

# Thrombus Imaging Research

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## Radiolabeled Antibodies

- Also under investigation

Platelet Imaging in Man using Antiplatelet  
Monoclonal Antibodies

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A. C. Perkins, R. J. Lonsdale

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*Platelets* (1993) 4, 123-128

- Large complex molecules with potentially slower background clearance



# Thrombus Imaging

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## Unmet Need

**A rapidly clearing marker  
of acute venous thrombosis**



# AcuTect™

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## Technetium Tc 99m Apcitide

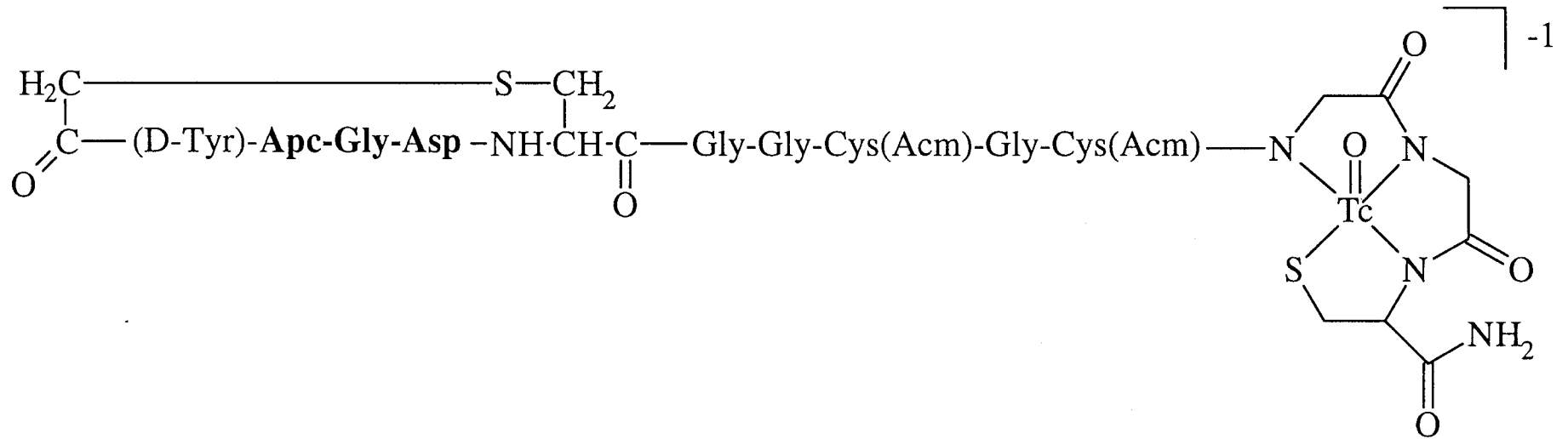
- 13 amino acid peptide = apcitide
- binding region for the platelet GPIIb/IIIa receptor
- Tc-99m complex





# AcuTect™

## Technetium Tc 99m Apcitide



AMGEN INC.

# AcuTect™

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## Active Binding Region

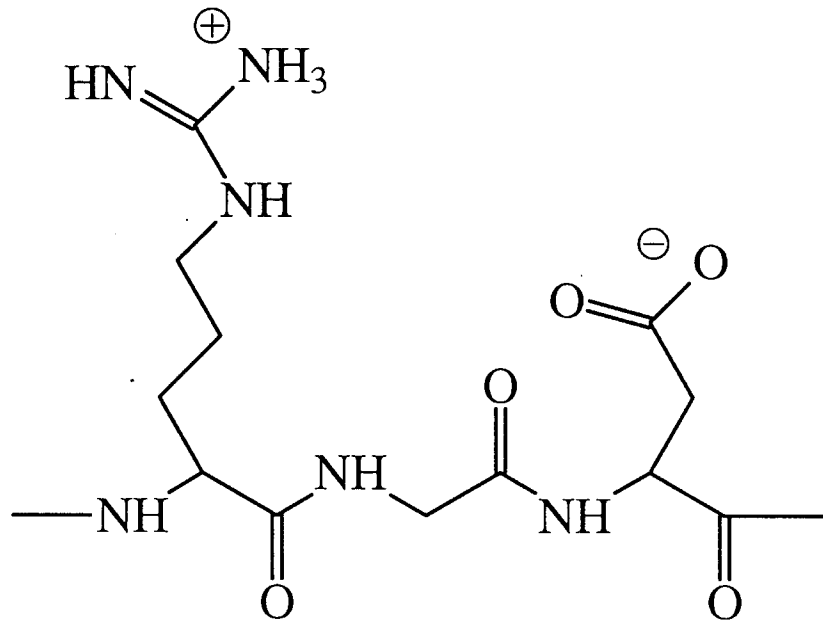
- analog of Arg-Gly-Asp (RGD)
  - 4 RGD sequences in fibrinogen
  - RGD binds to GPIIb/IIIa receptor on platelets
- Arg replaced with a synthetic amino acid (Apc)



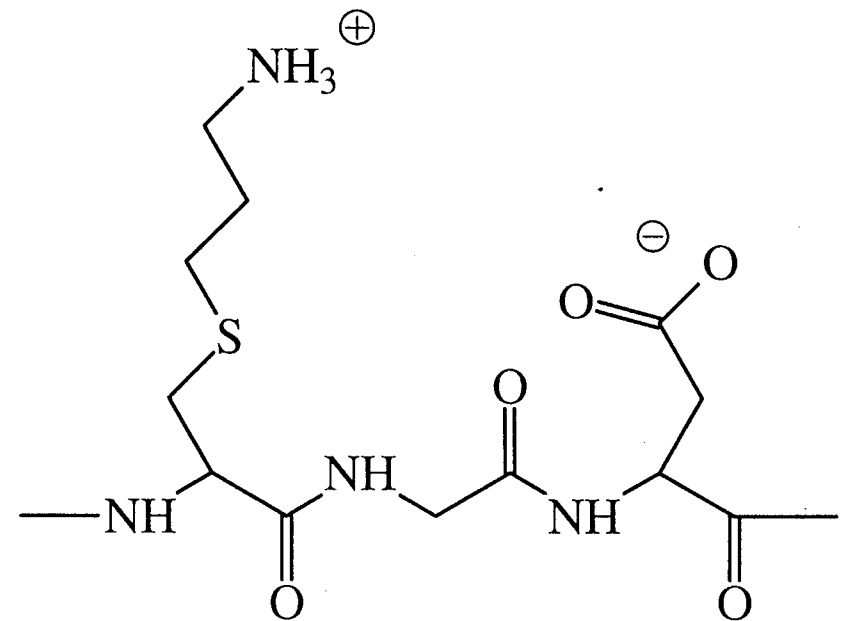
# AcuTect™

## Active Binding Region

RGD



AcuTect™



# AcuTect™

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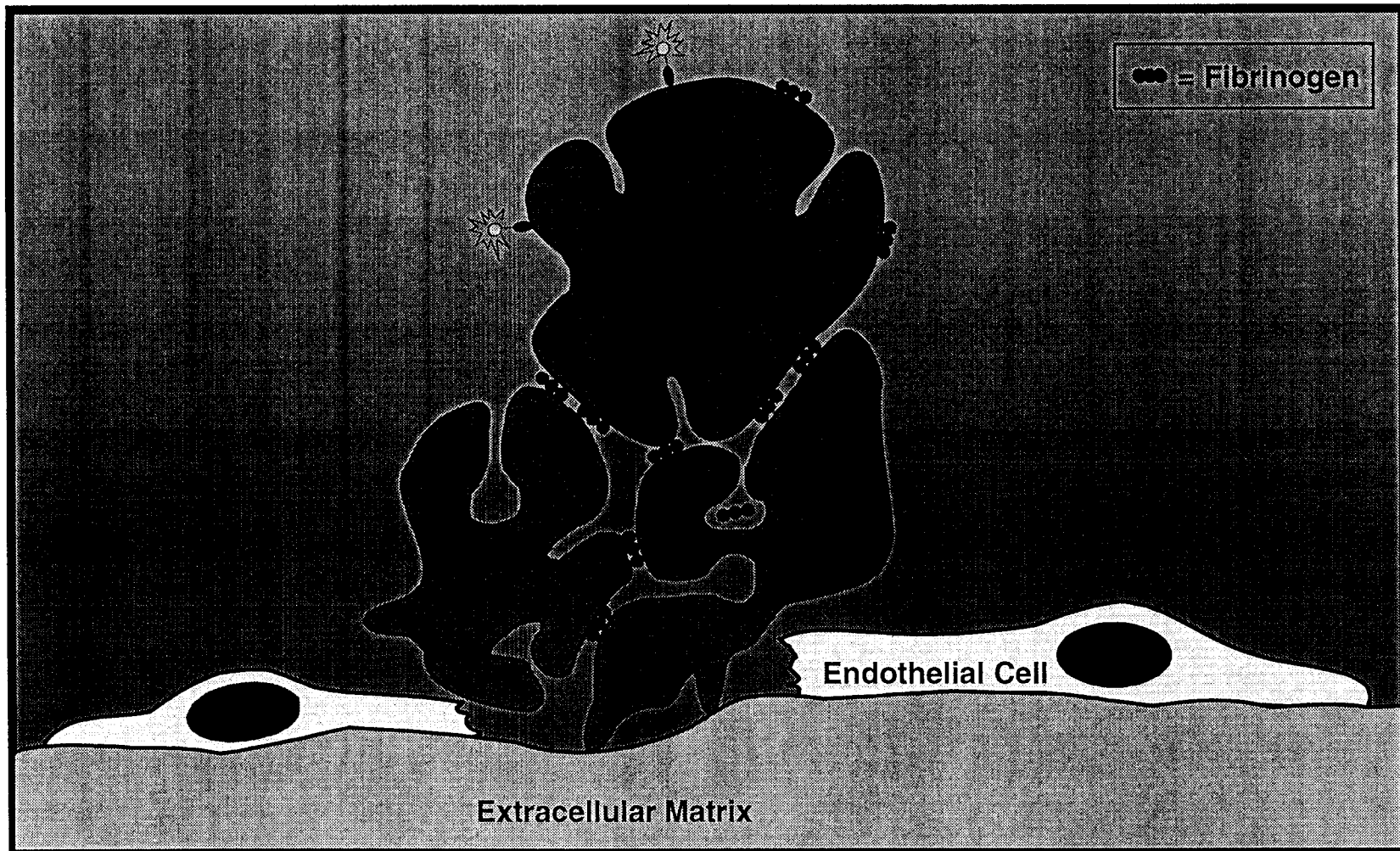
## GPIIb/IIIa Receptor

- expressed only on platelets
- not expressed on endothelial cells
- key in platelet aggregation
  - mediates the binding of fibrinogen to platelets
  - only binds fibrinogen when platelet activated



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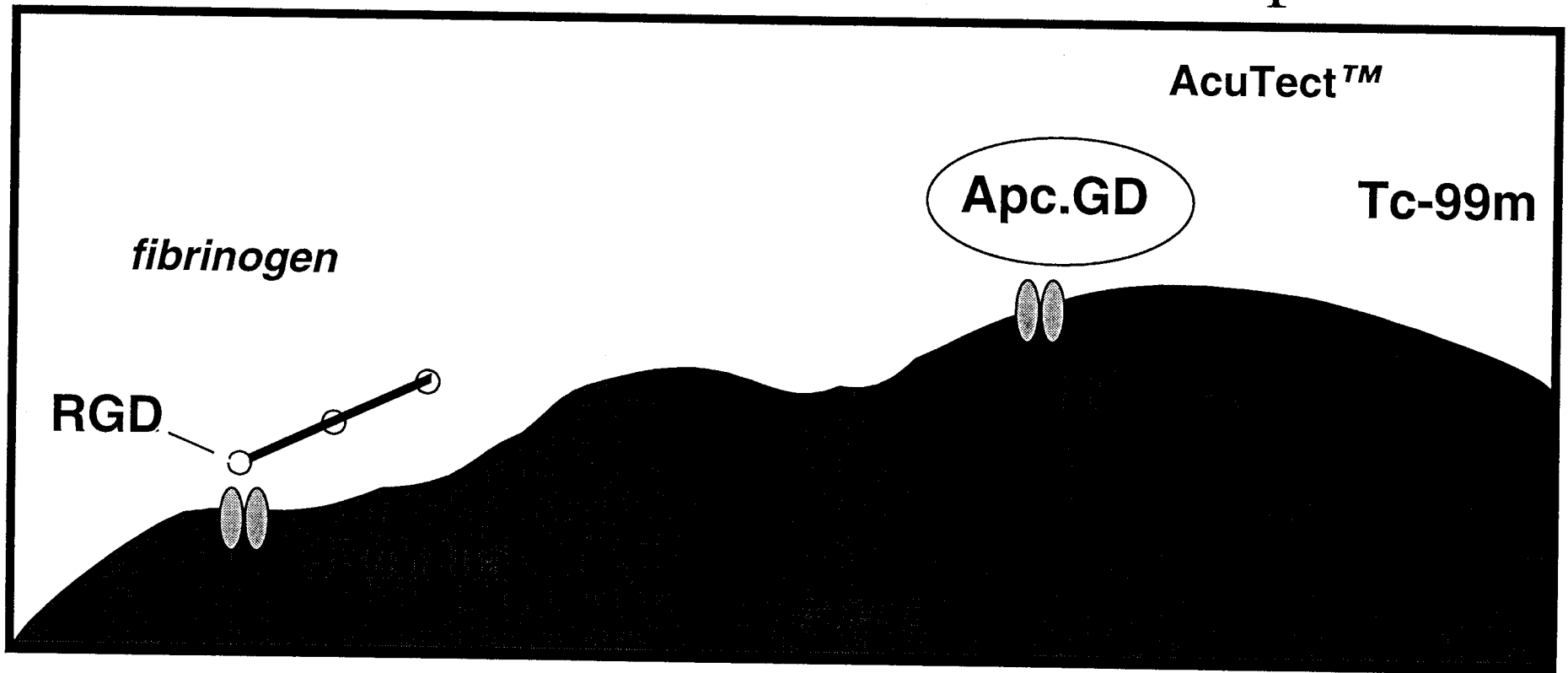
# Platelet Aggregation



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# AcuTect™ BEST POSSIBLE COPY

## Binding to Platelet GPIIb/IIIa Receptors



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# AcuTect™

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## Why It Should Work

- platelets are involved in acute but not chronic venous thrombosis
- AcuTect™ binds to platelets



# Deep Vein Thrombosis

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- origin
- platelet deposition
- fibrin/enmeshed blood cells
- propagation proximally - platelets/fibrin
- embolization
- organization

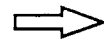
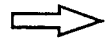
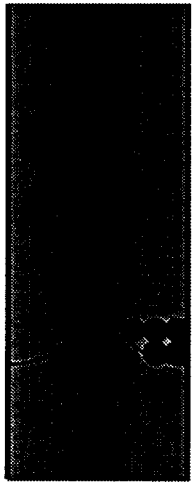




# Deep Vein Thrombosis

## Natural History

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or



platelets

thrombus

propagation

embolization

organization

*acute*

*chronic*

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# Acute Venous Thrombosis

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## Characteristics

- often non-occlusive
- proximal extension of initial thrombus
- unorganized, fragile
- high potential of embolization

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# Acute Venous Thrombosis

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## Platelets

- incorporated in acute thrombosis
- activated at thrombus
- express GPIIb/IIIa receptor
- normal GPIIb/IIIa ligand is fibrinogen



# AcuTect™

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## How It Works

- binds to GPIIb/IIIa receptors on activated platelets
- no binding to endothelial cell (vitronectin) receptors
- no binding to RBC or WBC
- fast clearance



# AcuTect™

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## GPIIb/IIIa Receptor Binding Affinity

- inhibits binding of fibrinogen to GPIIb/IIIa receptors with  $IC_{50} = 1.8 \text{ nM}$
- fibrinogen  $K_i$  for platelets = 120 nM



# AcuTect™

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## Receptor Specificity

- Vitronectin receptor expressed on platelets and endothelial cells
- NO BINDING of AcuTect™
- No inhibition of binding of vitronectin to its receptor at 1000 nM
- selectivity conferred by modified binding region



# AcuTect™

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## Inhibition of Platelet Aggregation

- GPIIb/IIIa receptor dependent process
- Inhibition of ADP-induced platelet aggregation in plasma
- Apcitide inhibits platelet aggregation
- $IC_{50} = 0.38 \mu M$



# AcuTect™

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## Effect of Anticoagulants

- no effect of aspirin on *ex vivo* inhibition of platelet aggregation by AcuTect™
- no effect of 0.6 U/mL heparin on *in vitro* inhibition of platelet aggregation by AcuTect™





# AcuTect™

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## Technetium Tc 99m Apcitide Binding to Human Platelets

- 3 times greater binding to activated platelets than to resting platelets



# AcuTect™

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## *In Vivo* Thrombus Uptake

- dog model
- external images
- thrombus-to-blood = 4
- thrombus-to-muscle = 11



# AcuTect™

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## Immunogenicity

- non-immunogenic in guinea-pig study
- no immune response in Phase I clinical study



# AcuTect™

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## Summary

AcuTect™ should and does bind specifically to  
acute venous thrombi



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# CLINICAL STUDIES

AcuTect™

DIATIDE, INC.

# ACUTECT™ CLINICAL STUDIES

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- Richard T. Dean, Ph.D. *CEO & Chief Scientific Officer*  
Diatide, Inc.
- Chris Nicodemus, M.D. *Vice President Clinical Operations*  
Diatide, Inc.
- John Lister-James, Ph.D. *Senior Director R&D*  
Diatide, Inc.
- Raymond Taillefer, M.D. *Chief of Nuclear Medicine and  
Clinical Investigator*  
Hopital Hotel Dieu De Montreal
- Jeffrey Ginsberg, M.D. *Director, Thromboembolism Unit*  
Hamilton Health Science Corp.

# CLINICAL PROGRAM

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	<u>Studies</u>	<u>Patients</u>
Phase 1	2	30
Phase 2	6	138
Phase 3	5	542
TOTAL	13	710

# SAFETY

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All Subjects (N=710)  
AEs Occurring in More Than 1 Subject

AEs - All Causes (%)

## Body

Pain	1
Headache	<1
Fever	<1

## Cardiovascular

Hypotension	<1
Tachycardia	<1

## Nervous

Hypertension	<1
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# SAFETY

## Treatment-Related Adverse Events Associated With AcuTect™ Imaging or Venography (Pivotal Studies)

	AcuTect™ N=278	Venography N=272	
<b>Body</b>			
Pain	0	3	
Asthenia	0	1	
Injection site edema	0	1	
Injection site reaction	0	1	
<b>Cardiovascular</b>			
Hypotension	1	0	
Syncope	0	1	
<b>Digestive</b>			
Nausea	0	2	
Vomit	0	1	
<b>Nervous</b>			
Hypesthesia	0	1	
<b>Skin</b>			
Rash	0	1	
<b>TOTAL</b>	<b>1</b>	<b>12*</b>	<b>*p &lt; 0.001</b>

ACUTECT™

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PIVOTAL TRIAL DESIGN

DIATIDE, INC.

# VENOUS THROMBOSIS

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## Product

## Measures

AcuTect™

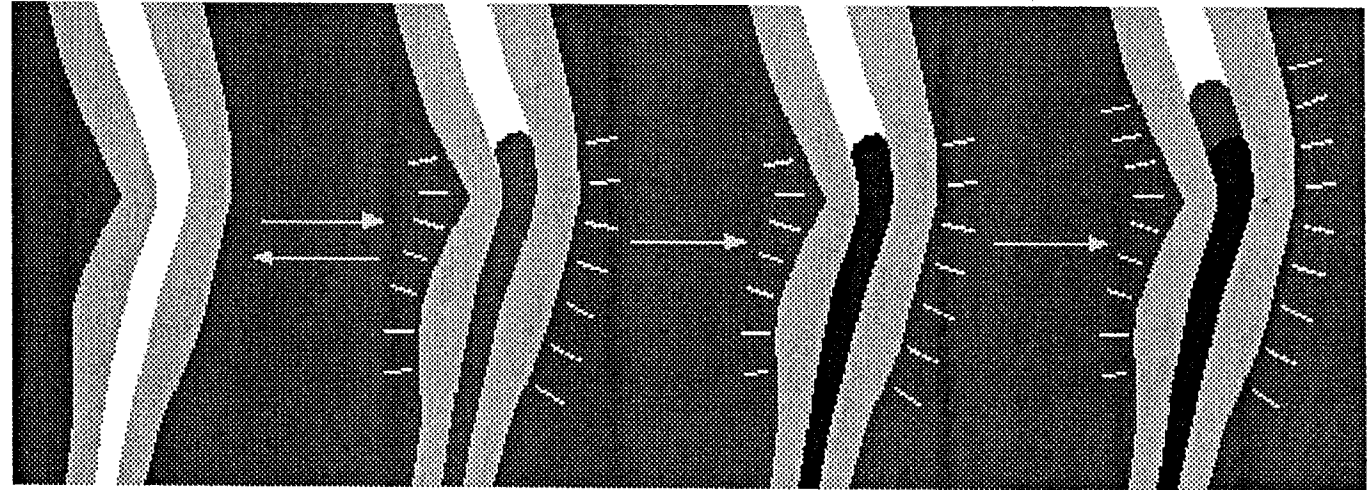
Biology - Acute Clot

Venography

Object - Flow Disturbance

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# ACUTE DVT DIAGNOSIS



Normal

Acute

Chronic

Acute and Chronic

AcuTect™

-

+

-

+

Anatomical  
Test

-

+

+

+

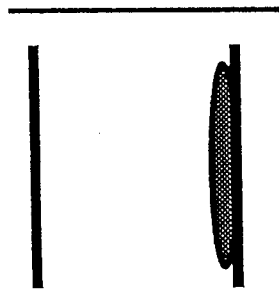
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# RESULTS POSSIBLE

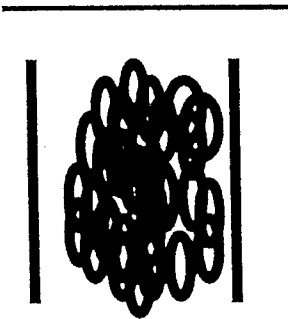
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1



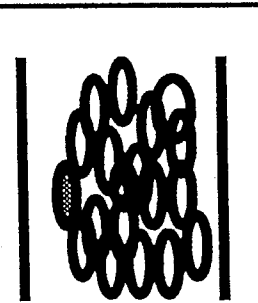
**Non-  
Occlusive**

2



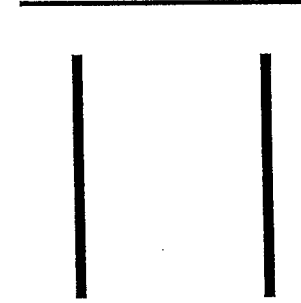
**Recent**

3



**Old**

4



**No**

AcuTect +

CV -

FP

AcuTect +

CV +

TP

AcuTect -

CV +

FN

AcuTect -

CV -

TN

# STABLE DATUM

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AcuTect™ and Venography Will Have  
Highest Concordance in Acute Disease

APPEARS THIS WAY  
ON ORIGINAL

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# PATIENT ELIGIBILITY - PIVOTAL PROTOCOLS

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Each Patient Evaluated with  
Venography and AcuTect™

- Within 10 days of onset of signs/symptoms
- Or within 10 days of surgery

# EFFICACY CRITERIA

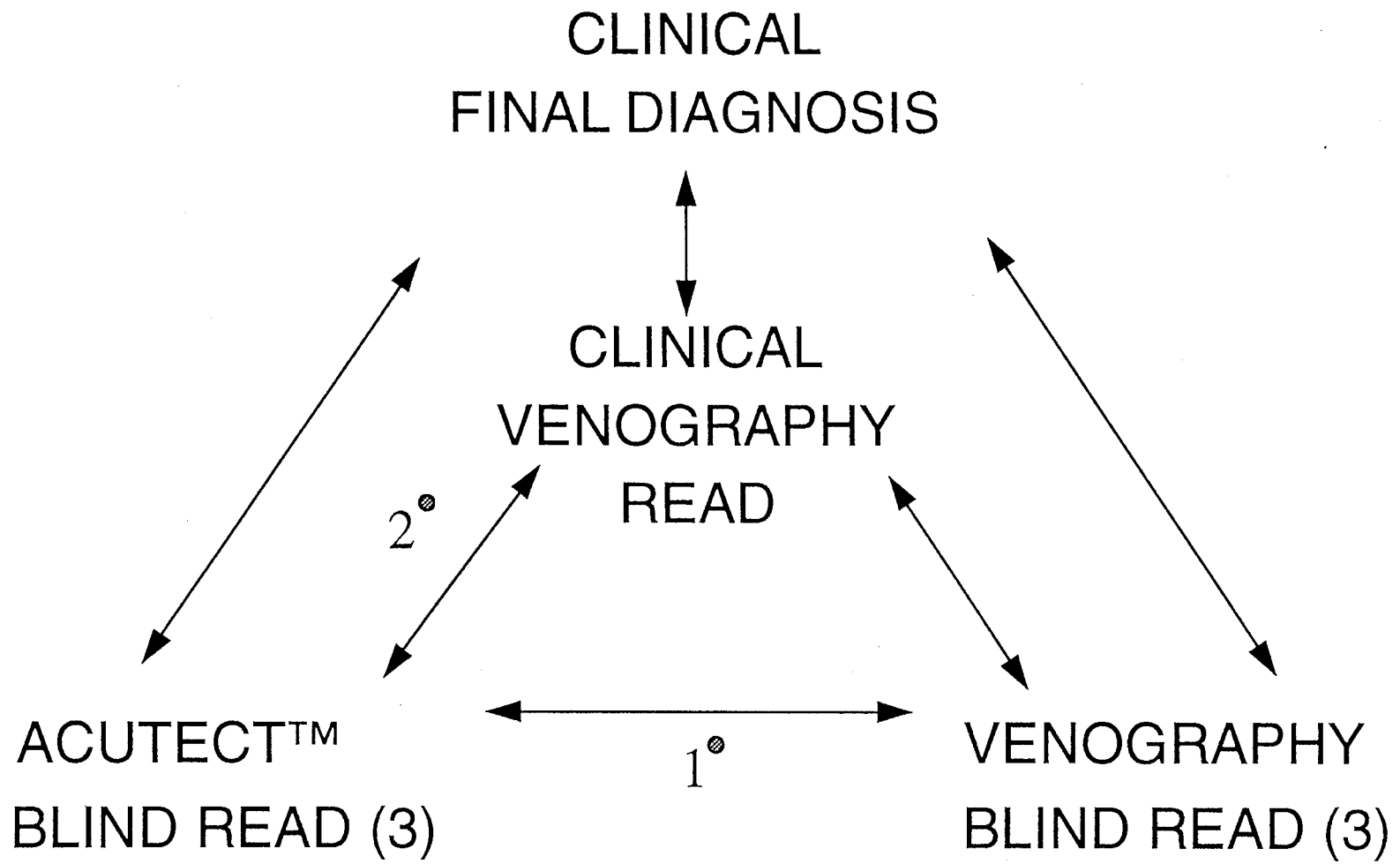
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- Target Blind-Read Agreement: 75%
- Confidence Interval Lower Limit: 60%



# ENDPOINTS

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# VENOGRAM IMAGE EVALUATIONS

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- Institutional Read
- Three Certified Radiologists Blind to Clinical Information

APPEARS THIS WAY  
ON ORIGINAL

# INDEPENDENCE OF INSTITUTION VENOGRAPHY READ TO ACUTECT™ RESULT

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*% of Venograms Documented  
Read Prior to AcuTect™ Test*

Study A	74
Study B	86

- Follow-up documented venograms read after AcuTect™ test were without prior knowledge of result

# ACUTECT™ IMAGE EVALUATIONS

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- Institutional Read
  
- Three Nuclear Medicine Physicians  
Blind to Clinical Information
  - Read 1 - Combined Timepoints
  - Read 2 - Separate and Combined Timepoints  
(FDA requested)

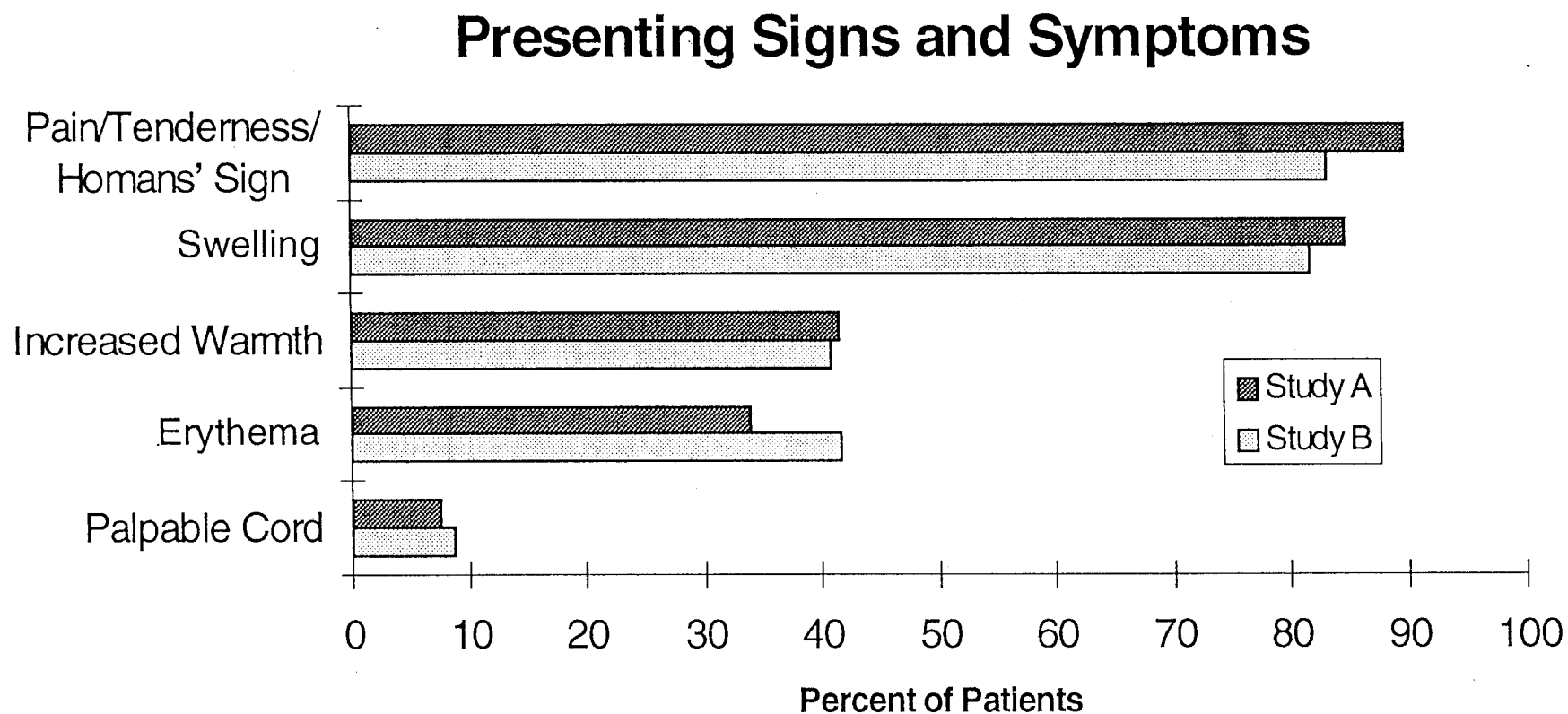
# DEMOGRAPHICS - PIVOTAL STUDIES

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	<b>32A</b> (N=118)	<b>32B</b> (N=125)
Age (yr)		
Mean	59.8	59.4
Weight (kg)		
Mean	81.1	76.1
Height (cm)		
Mean	168.7	168.9
Gender		
Female	60	63
Male	58	62
Race		
Asian	2	2
Black	2	5
Caucasian	111	111
East Indian	1	4
Hispanic	1	3
Native American	1	0

# PRESENTING SIGNS AND SYMPTOMS

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# CLINICAL BACKGROUND OF STUDY POPULATION

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	<u>32A</u>	<u>32B</u>
Prior Thrombotic History	20%	28%

APPEARS THIS WAY  
ON ORIGINAL

# PHASE 3 EFFICACY RESULTS

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## Primary Endpoint

Agreement with Blind Read Venography

Study A	Met
Study B	Missed

## Secondary Endpoint

Inst. Venography Read

Study A	Met
Study B	Met

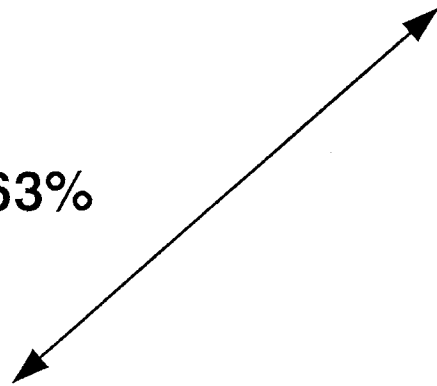


# COMPARISON OF AGREEMENT RATES

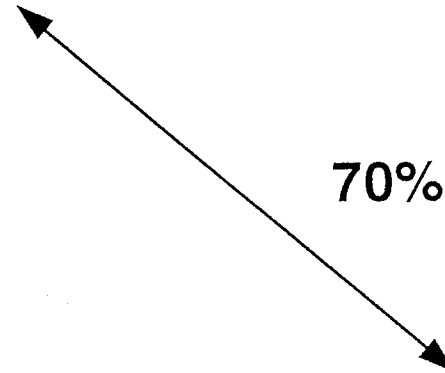
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Institutional Venography

63%



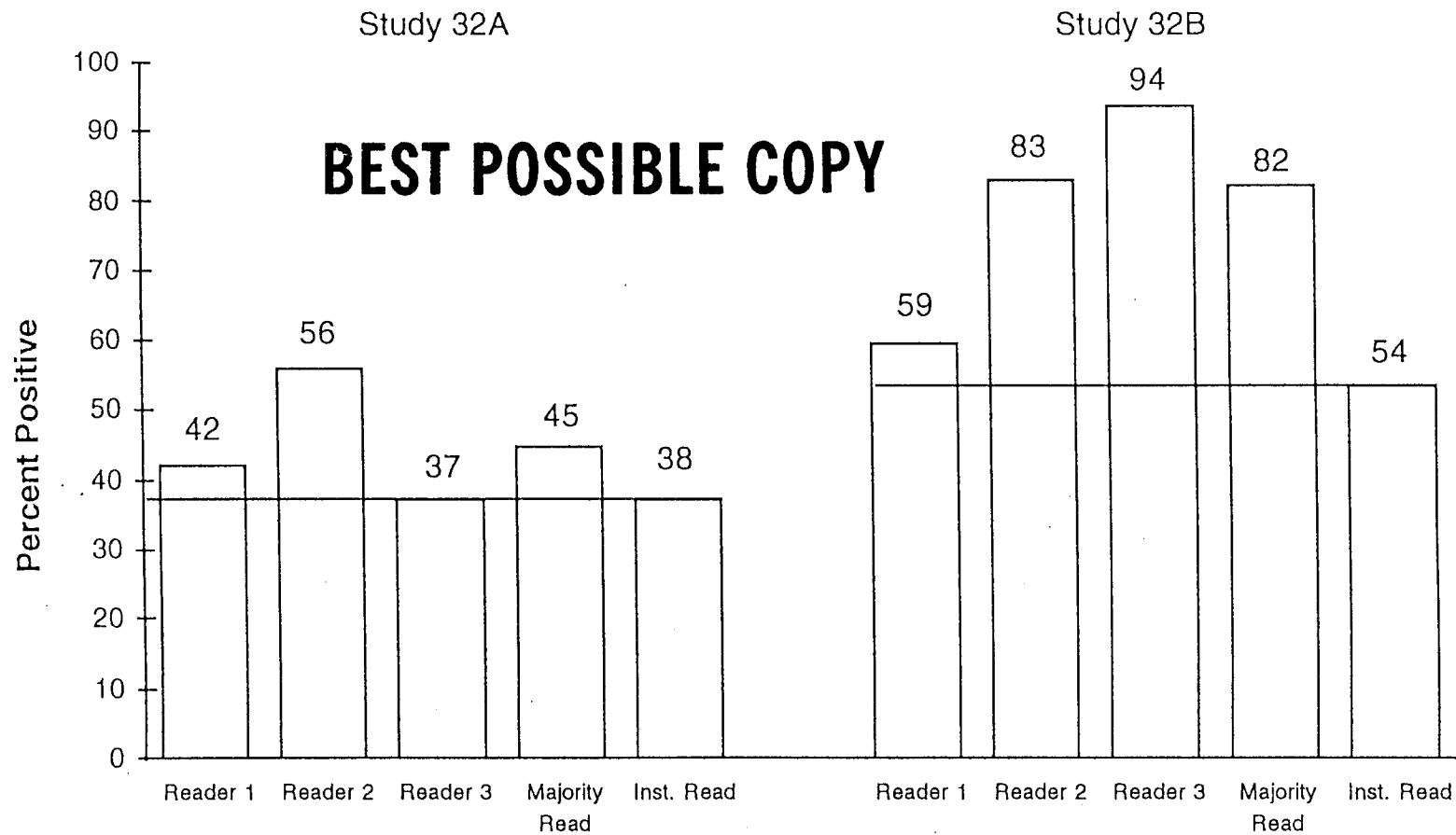
70%



Blind Read  
Venography

Blind Read  
AcuTect™

# ORIGINAL BLIND-READ CONTRAST VENOGRAPHY: PERCENT POSITIVE PATIENTS



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# STUDY B: COMPARISON OF VENOGRAPHY BLIND READERS 1 AND 3

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Agreement 63.6%

Confidence Interval Lower Limit 55.0%

P Value NS

# HAMILTON THROMBOSIS RESEARCH CENTER INDEPENDENT BLIND READ OF VENOGRAMS

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- Vascular Medicine Center of Excellence
- Venography is Institutional Standard of Practice
- Reading Criteria and Procedure for Interpretation of Venography Truth Standards in Place
- Validated in Treatment Studies
- FDA Approved Products: Lovenox<sup>®</sup> and Normiflo<sup>®</sup>

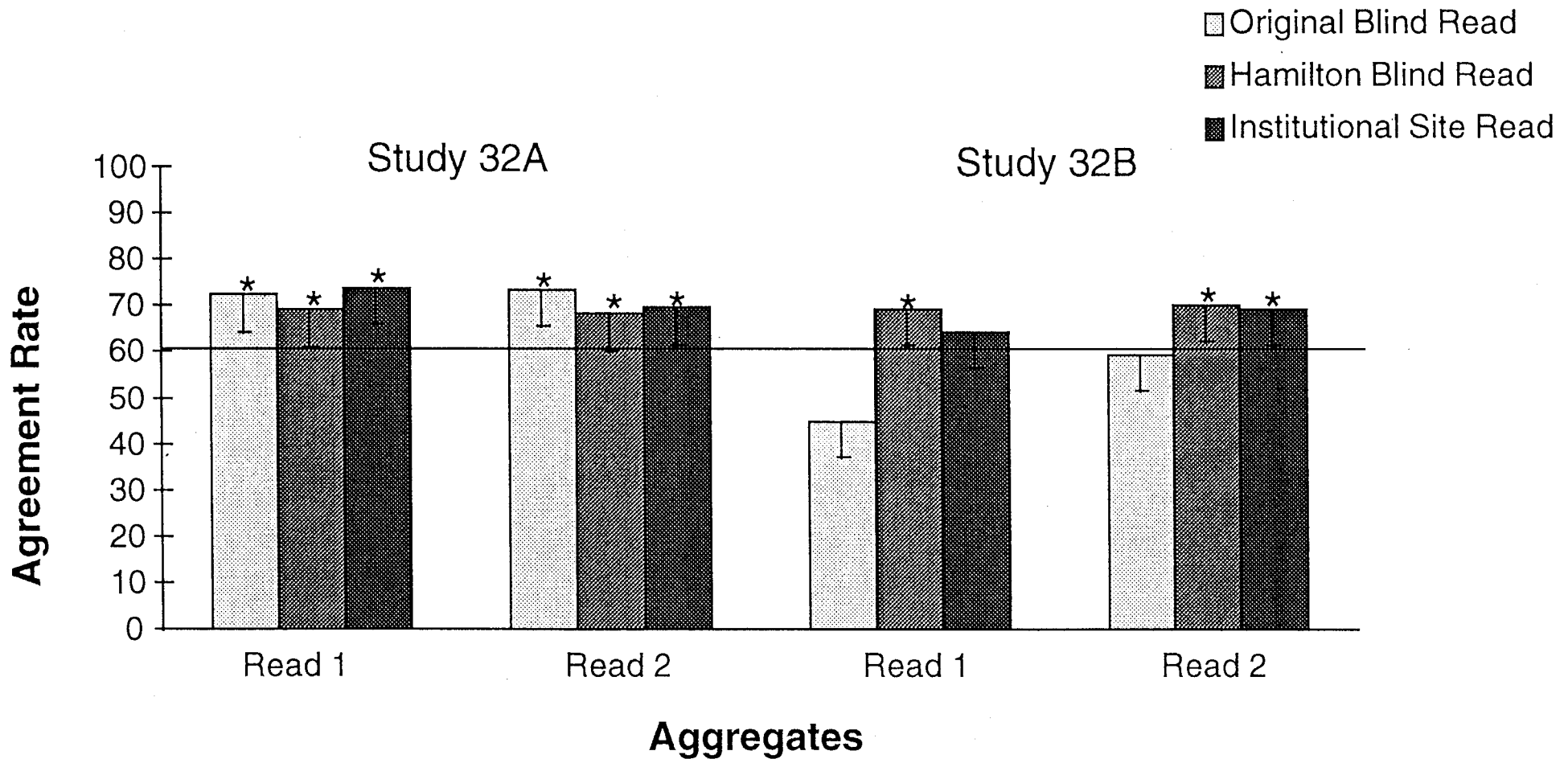
# AGREEMENT RATES WITH INSTITUTIONAL VENOGRAPHY READS

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<b>Study</b>	<b>Hamilton Blind Read Venography</b>	<b>Original Blind Read Venography</b>
32A	80%	66%
32B	75%	61%

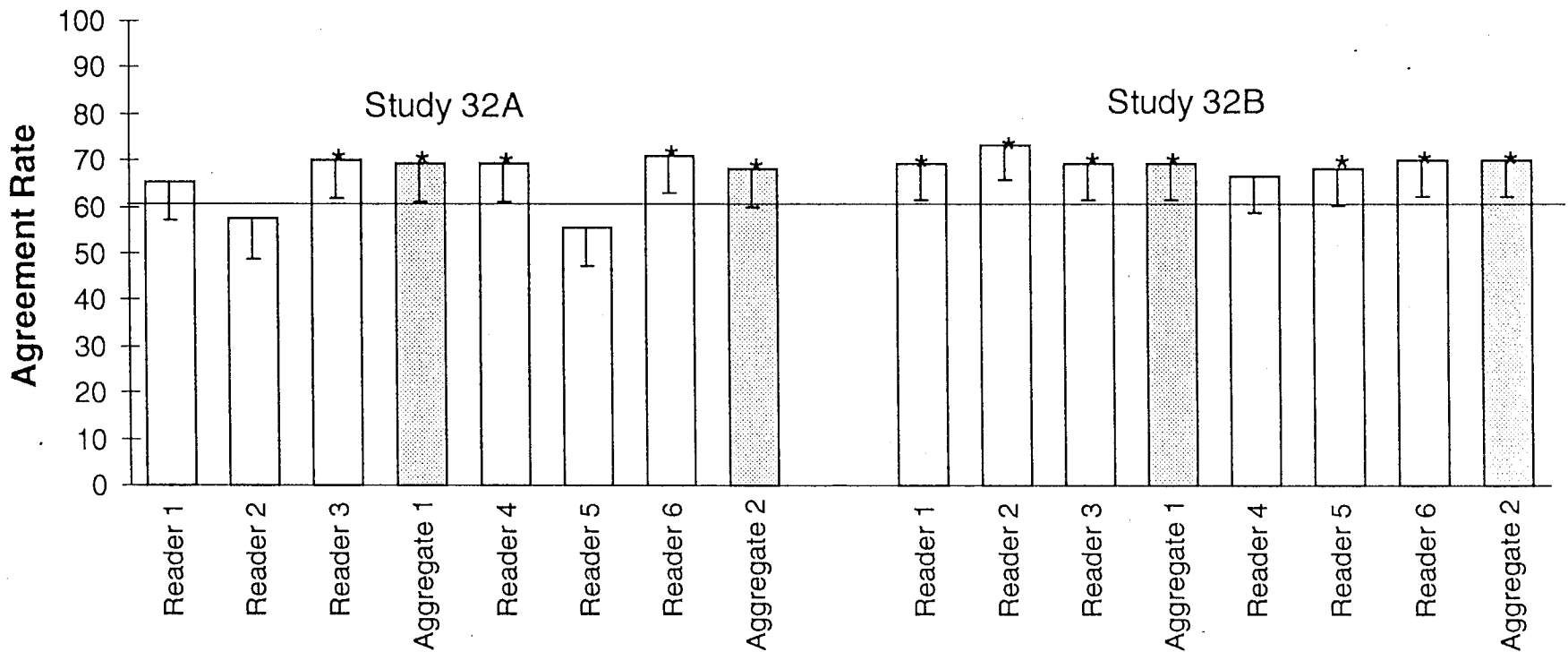
APPEARS THIS WAY  
ON ORIGINAL

# ACUTECT™ BLIND READ AGREEMENT RATES



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# AGREEMENT RATES FOR EACH BLINDED ACUTECT™ READER RELATIVE TO HAMILTON BLIND READ

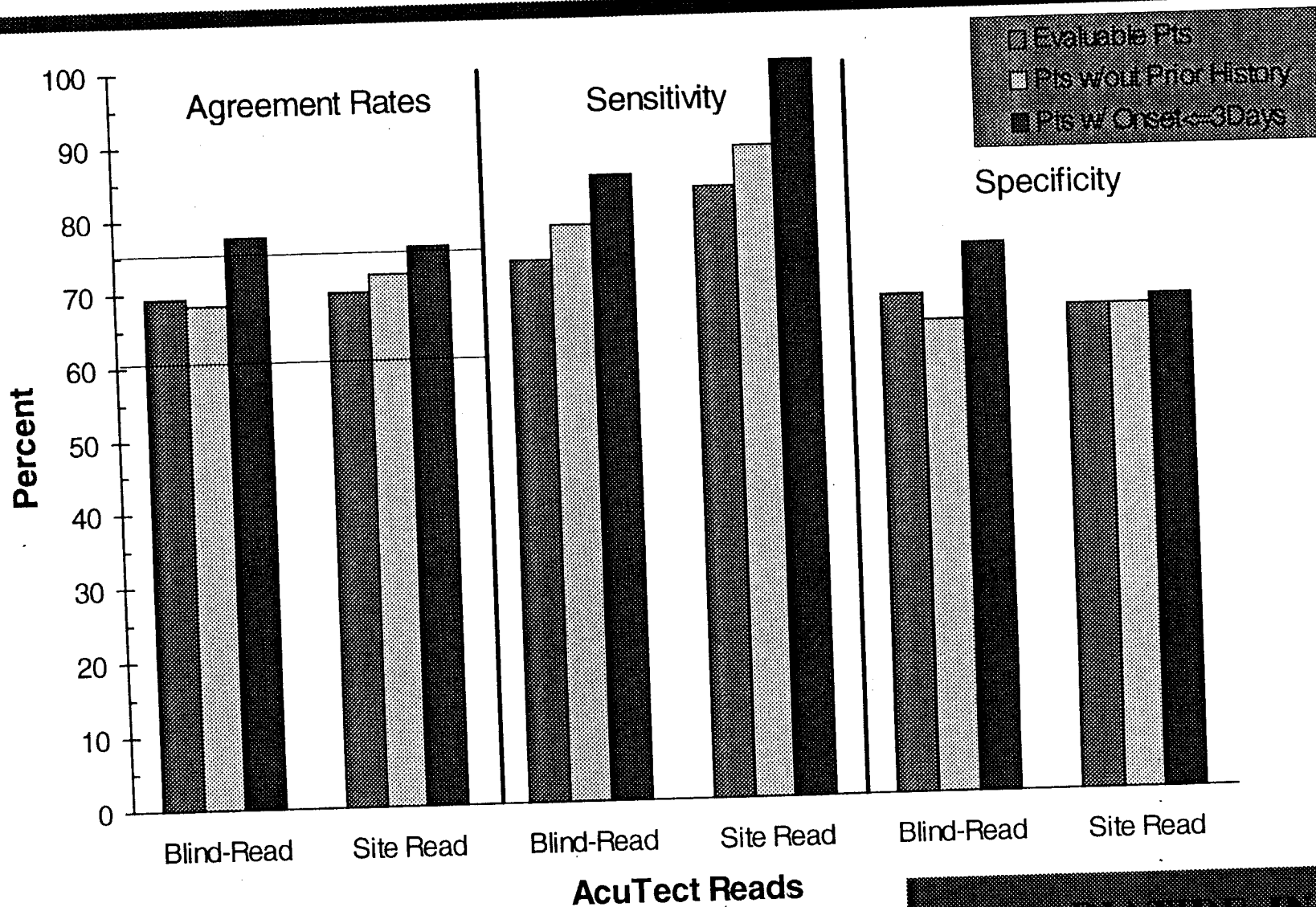


\* $p < 0.05$

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# SUBSET ANALYSES: COMBINED STUDIES VS HAMILTON BLIND READ



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# AGREEMENT RATES - USE/NO USE OF ANTITHROMBOTICS

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Anticoagulation Does Not Affect AcuTect™  
Performance Agreement Rate

Concomitant Medication	Patient Population	Agreement Rate
Any Antithrombus Medication	Users	70%
Heparin	Non-Users	68%
	Users	69%
	Non-Users	69%

# RISK OF POTENTIAL BIAS IN “POST HOC” ANALYSIS

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- This is a methodological problem
  - What is Truth?
- Hamilton produces the best measure of Truth
  - Blinded to clinical and Acutect<sup>TM</sup> results
- Acutect<sup>TM</sup> images were not the subject of a retest
- Prevalence consistent with published results



# ACUTECT™ EFFICACY

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- Blind Read Venography - Study B Flawed by Unexpectedly High Positivity
- Hamilton Blind Read Validates Consistency of Study Populations and Performance of AcuTect™
- AcuTect™ Meets Efficacy Criteria Based on Hamilton Blind Read
  - Treatment Validated
  - Used for FDA Approval of Therapeutic Products: Lovenox® and Normiflo®

# CONCLUSION

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AcuTect™ is Safe and Effective for  
Diagnosis of Acute Venous Thrombosis

APPEARS THIS WAY  
ON ORIGINAL

BIATIDE, INC.

# PROPOSED INDICATION

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AcuTect™ is indicated for the scintigraphic imaging of acute venous thrombosis.

