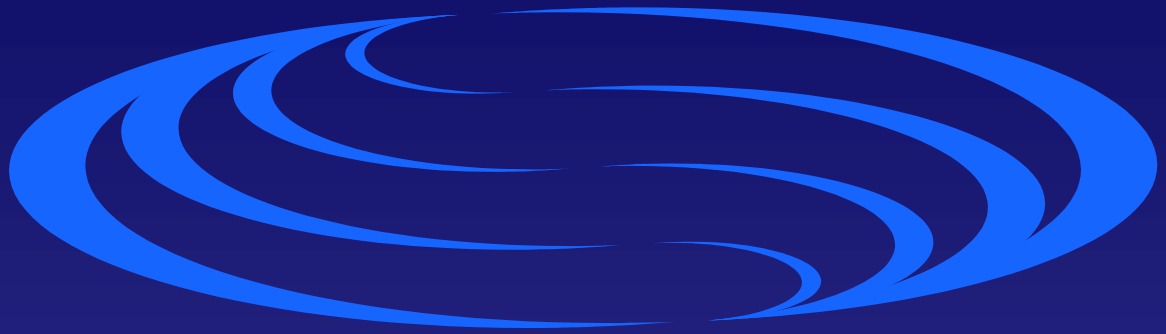
# FDA Medical Imaging Drugs Advisory Committee

**July 10, 2000**

**BLA 99-1407**
**LeuTech®**

**Palatin Technologies, Inc.**



# PALATIN

## TECHNOLOGIES, INC.

CP001.01

# Palatin Presenters

| | |
|---|---|
| Charles Putnam | Chief Operating Officer<br>Palatin Technologies, Inc. |
| Terry Smith, Ph.D. | Executive Director of<br>Product Development<br>Palatin Technologies, Inc. |
| Eric Rypins, M.D. | Department of Surgery<br>Tri-City Medical Center |
| Samuel Kipper, M.D. | Director of Nuclear Medicine<br>Tri-City Medical Center |
| Karen McElvany, Ph.D. | Director of Clinical Affairs<br>Certus International, Inc. |

# Additional Palatin Consultants

| | |
|---|---|
| Robert Carretta, M.D. | Sutter-Roseville Medical Center<br>Roseville, California |
| Christopher Palestro, M.D. | Long Island Jewish Medical Center<br>New Hyde Park, New York |
| Mathew Thakur, Ph.D. | Thomas Jefferson University<br>Philadelphia, Pennsylvania |
| M.B. Khazaeli, Ph.D. | Univ. of Alabama<br>Wallace Tumor Institute<br>Birmingham, Alabama |
| Kathleen Madsen, Ph.D. | Certus International, Inc.<br>Chesterfield, Missouri |

# LeuTech®
## MIDAC Meeting Agenda

| | |
|---|---|
| Introduction | C. Putnam |
| Description of LeuTech | T. Smith, Ph.D. |
| Equivocal Appendicitis | E. Rypins, M.D. |
| Imaging Techniques and Interpretation | S. Kipper, M.D. |
| Clinical Development Program | K. McElvany, Ph.D. |
| Conclusion | C. Putnam |

# Palatin Technologies, Inc.

- Biopharmaceutical company, established in 1996
- Two products currently under development
  - PT-141 cyclic melanocortin peptide for treatment of erectile dysfunction
  - LeuTech radioimaging agent for equivocal appendicitis

# LeuTech

- Murine IgM monoclonal antibody specific to the CD-15 antigen found on the surface of human neutrophils
- Potential utility as a white blood cell imaging agent with advantages relative to existing WBC agents
  - In-vivo labeling
  - No blood handling
  - Fast Results
  - No opportunity for reinjection errors

# Development History

- Developed by Dr. Mathew Thakur in 1989
- First human clinical use in 1990
  - Proof of concept in various infections
  - Physician sponsored IND
- Palatin sponsored IND submitted 1997
- Initial indication: appendicitis with equivocal signs and symptoms
  - Commonly occurring condition
  - Need for additional diagnostic information
  - Rapid and certain confirmation of diagnosis (histopathology)
- Biologics License Application submitted in November 1999

# LeuTech - Additional Studies

- Osteomyelitis - prosthetic joint infections
- Osteomyelitis - diabetic foot ulcers
- Post-surgical infection
- Inflammatory bowel disease

# LeuTech - Proposed Indication

Scintigraphy with Technetium Tc 99m Anti-CD15 Antibody is indicated for the diagnosis of appendicitis in patients with equivocal signs and symptoms. It is useful to rule out appendicitis in patients presenting with equivocal diagnostic evidence.

# LeuTech

- Accurate in patients presenting with equivocal signs and symptoms of appendicitis
- Safe - no significant adverse reactions
- Improves patient management

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# Characteristics of LeuTech

LeuTech is a Tc 99m labeled antibody which binds *in vivo* to human neutrophils and is useful for imaging infection.

- Specific to CD15 antigens
  - Binds avidly ($K_d = 10^{-11}$ M)
  - Abundant binding sites (~ $5.1 \times 10^5$ antigens per PMN)
- No change in chemotaxis, phagocytosis, or adherence of neutrophils at indicated dosage

# Properties of LeuTech

- Pentameric IgM monoclonal antibody
- Produced in cell culture from hybridoma cell line
- Molecular weight 970,000 Daltons
- Distribution $T_{1/2}$ of 18 minutes and elimination $T_{1/2}$ of 8 hours
- 14% to 50% of circulating radioactivity is bound to PMNs.

# Contents of LeuTech Kit

- Vial, containing 250 µg of lyophilized antibody
  - Maltose, monohydrate
  - Succinic Acid, ACS
  - Sodium Potassium Tartrate, tetrahydrate, USP
  - Glycine, USP
  - Disodium EDTA, dihydrate, ACS
  - Stannous Tartrate
- Ampoule of ascorbic acid solution

# Preparation of LeuTech

- Add 20 - 40 mCi of pertechnetate to lyophilized antibody
  - Incubate 30 minutes at 37° C
  - Add ascorbic acid solution
- Labeling efficiency > 90%
  - Tested by ITLC
  - Mean labeling efficiency = 96.9%

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# Demographics of Appendicitis
## CDC Division of Bacterial Diseases
## Center for Infectious Disease (1990 CDC Report)

- Most common cause of abdominal pain requiring surgery.
- Excluding trauma, most frequently encountered condition requiring emergency surgery in both adults and children
- 250,000 new cases of appendicitis per year
- Peak incidence in second and third decades of life
- Lifetime risk of appendicitis is 7%
- Negative laparotomy rates range from 10% to 30%
  - Higher in certain populations (geriatric, pediatric)

# Statement of the Problem

- The classical picture of appendicitis is a young person with central abdominal pain that localizes to the right lower quadrant with guarding, anorexia, and leukocytosis.
- Up to 50% of patients with appendicitis present to the Emergency Department without classical signs and symptoms.
- Accurate and timely diagnosis is particularly difficult in
  - Early appendicitis
  - Reproductive age females
  - Pregnancy
  - Extremes of age

# Statement of the Problem

- Surgeons traditionally have three choices:
  - Send home: wrong for positive cases
  - Immediate surgery: wrong for negative cases
  - Admit and observe: not ideal for any case

- In equivocal cases, admission and observation is often the practice, with the following clinical consequences:
  - Unnecessary admission in patients without appendicitis
  - Delay in treatment in patients with appendicitis

# Statement of the Problem
## Patients without Appendicitis

- Unnecessary admission
- Unnecessary surgery

# Statement of the Problem
## Patients with Appendicitis

- Delay in treatment of appendicitis can lead to perforation and/or sepsis.
- If patients are sent home in error, they almost invariably return with perforated appendicitis.
- Perforation frequently results in increased morbidity and prolonged hospitalization.

# Current Imaging Modalities

- Ultrasonography
  - Highly operator-dependent
  - Diagnostic accuracy is highly variable
  - Low sensitivity (~50%) with perforation
- Helical Computed Tomography
  - High accuracy is possible
  - Optimal technique not standardized
    - Intravenous/oral contrast vs. contrast enema vs. no contrast
  - Lengthy or uncomfortable preparation may be required
- All existing modalities require morphological changes to make a diagnosis of appendicitis

# Conclusions

- Management of appendicitis remains a problem
- Current modalities have limitations
- LeuTech has the potential to improve the management of these difficult patients

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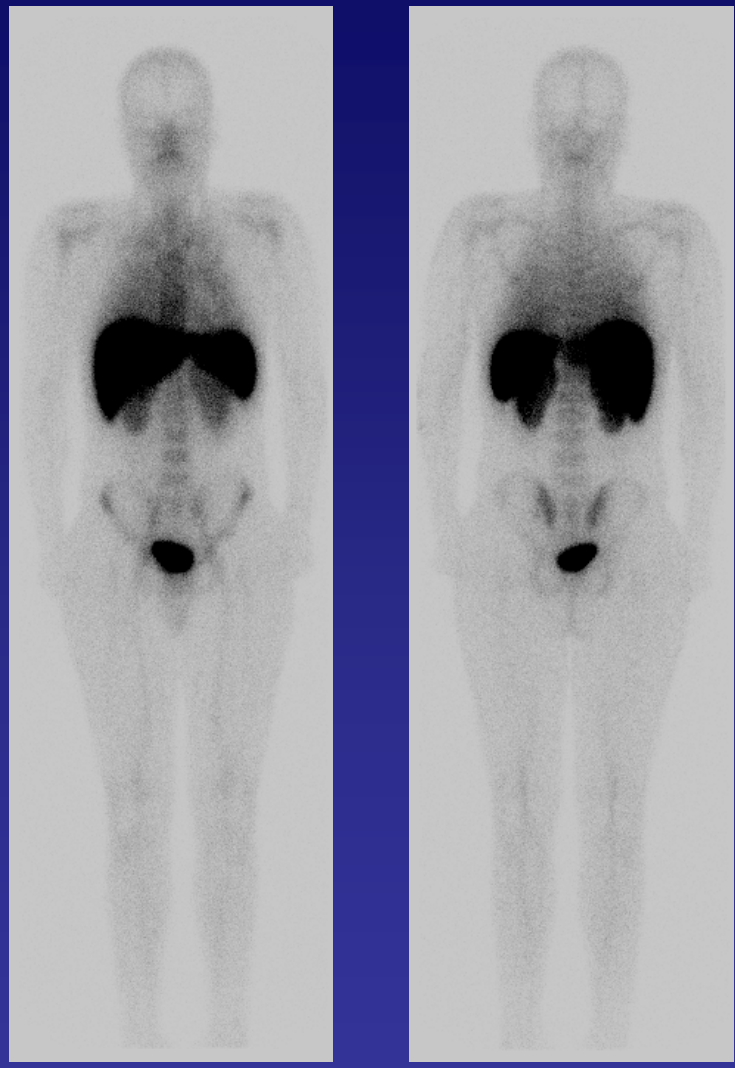
# LeuTech Imaging

- LeuTech imaging techniques were developed during the course of Phase 2 and implemented in the Phase 3 study in equivocal appendicitis patients
  - No patient preparation required
  - Supine patient position on imaging table
  - Gamma camera above abdomen and pelvis
  - Intravenous administration followed by immediate imaging
  - Sedation was not required in adults or children

# LeuTech Biodistribution

- Blood pool clearance is rapid but variable
- RE system: liver, spleen & bone marrow
- Urinary excretion: kidneys & bladder
- No intestinal or biliary excretion

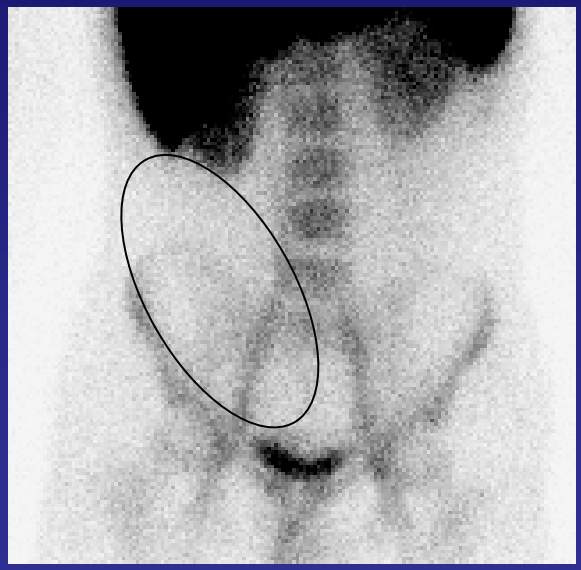
Phase 3 Patient A-33: 14 y.o. male



Anterior Posterior

2 Hours

# LeuTech Interpretation
## Appendicitis Zone



Anterior Static 72 min

Phase 3 Patient J-22: 15 y.o. male

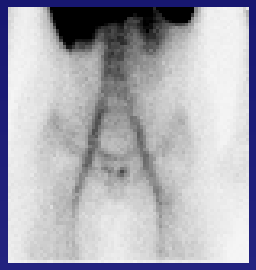
# LeuTech Interpretation
## Criteria for Appendicitis

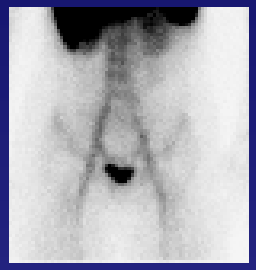
- Location: abnormal uptake of any intensity level with any distribution within the appendicitis zone
- Asymmetry: uptake on the right side is greater than that on the left
- Persistence: abnormal uptake does not disappear with time or positional changes

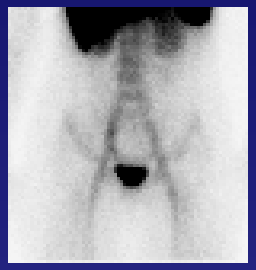
# LeuTech Interpretation
## Criteria for Negative Scan

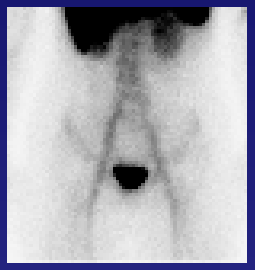
- Absence of abnormal persistent LeuTech accumulation within the “appendicitis zone”
- Presence of abnormal persistent LeuTech accumulation outside of the appendicitis zone was considered negative for appendicitis but positive for “other infection”

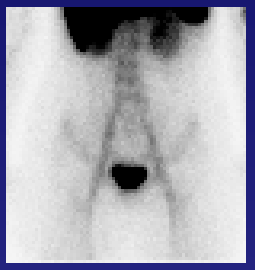
# Typical Dynamic Image Sequence
## Negative Scan

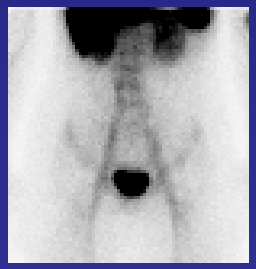

11 min


15 min

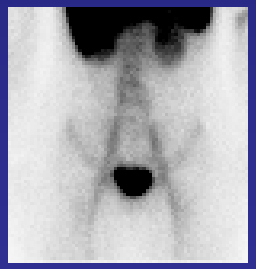

19 min

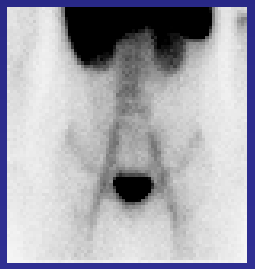

23 min

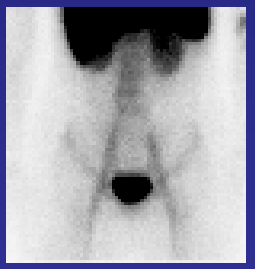

27 min


31 min


35 min

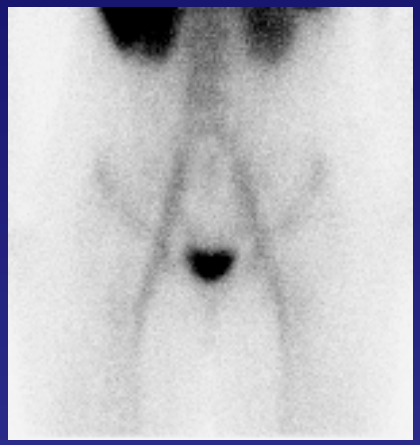

39 min


43 min

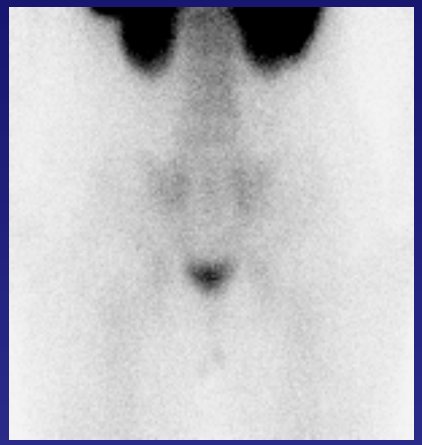

47 min

Phase 3 Patient A-03: 8 y.o. female

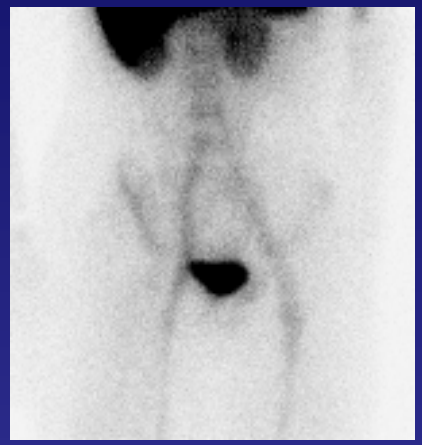
# Typical Static Image Sequence
## Negative Scan



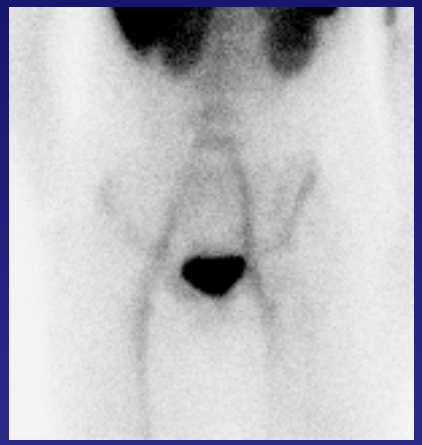
Anterior
59 min



Posterior
59 min



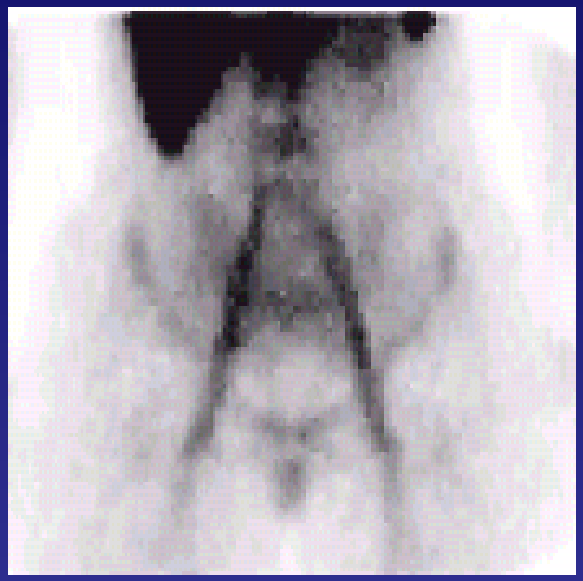
Right Anterior
Oblique
67 min



Left Anterior
Oblique
76 min

Phase 3 Patient A-03: 8 y.o. female

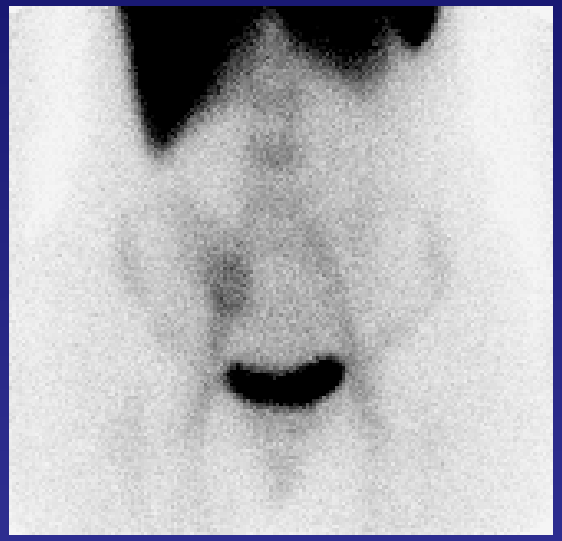
# Positive LeuTech Scan
## Focal Uptake Pattern



Dynamic Series 11 - 47 minutes

Phase 3 Patient A-8: 43 y.o. female

# Positive LeuTech Scan
## Focal Uptake Pattern



Anterior Static
61 minutes

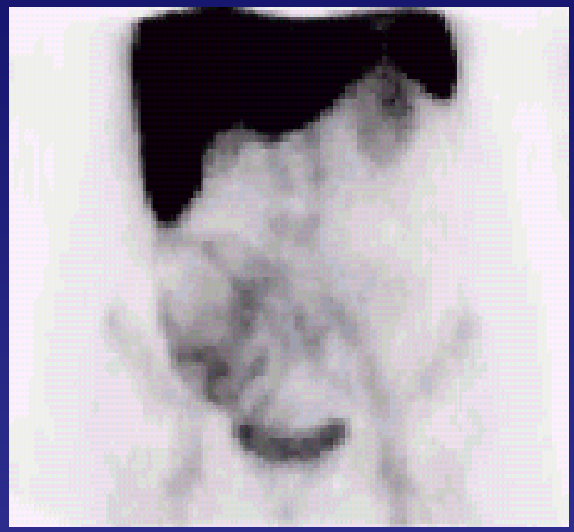
Phase 3 Patient A-8: 43 y.o. female, perforated appendix

# Positive LeuTech Scan
## Linear Uptake Pattern

Anterior Static 48 minutes

Phase 2 Patient A-32: 17 y.o. male, retrocecal appendix

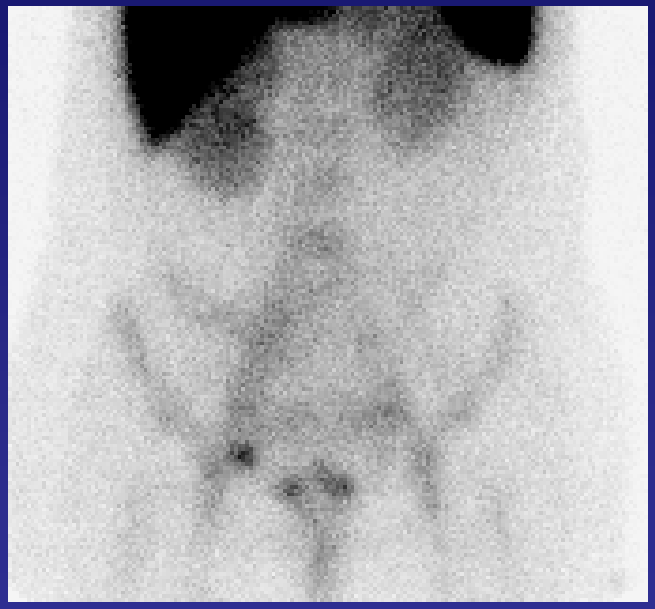
# Positive LeuTech Scan
## Diffuse Uptake Pattern



Dynamic Series 4 - 32 minutes

Phase 3 Patient H-14: 61 y.o. female, appendicitis with phlegmon

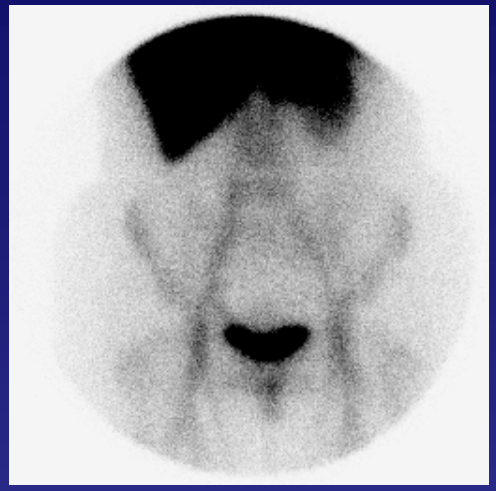
# Positive LeuTech Scan
## Perforated Appendix with Pelvic Abscess



Anterior Static 51 minutes

Phase 2 Patient A-01: 34 y.o. female

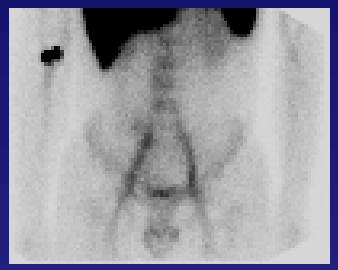
# Case Study 1



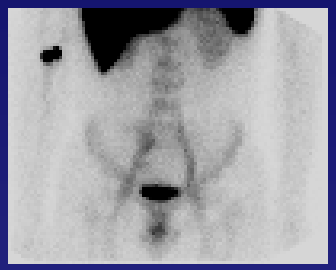
Anterior Standing Static
57 minutes

- Phase 3 Patient A-9: 26 y.o. female
- Initial plan: immediate surgery
- LeuTech scan: negative for appendicitis
- Post-scan plan: discharge home
- Final diagnosis: negative for appendicitis

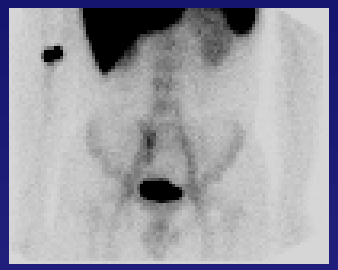
# Case Study 2



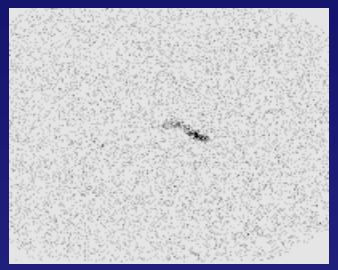
Anterior Dynamic 4 min



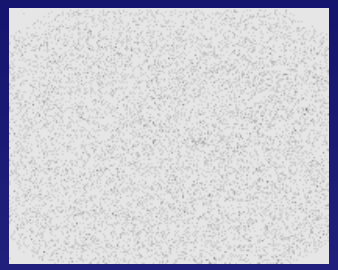
Anterior Dynamic 20 min



Anterior Dynamic 40 min



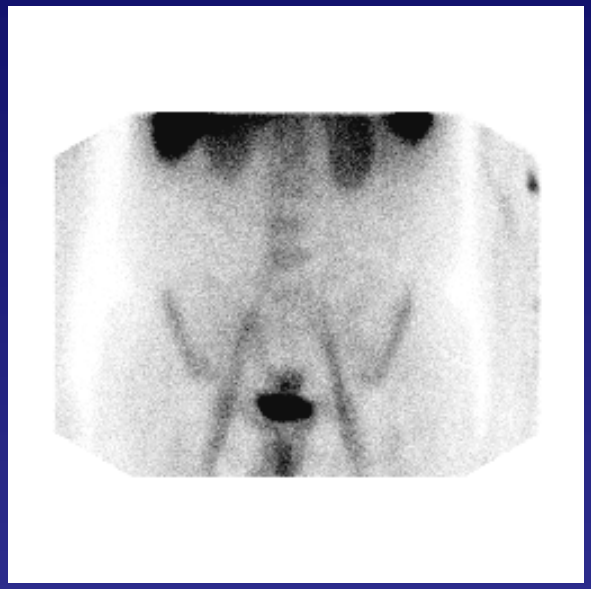
Appendix Specimen



Lymph Node Specimen

- Phase 2 patient A-26: 26 y.o. male
- Initial plan: send home
- LeuTech scan: positive for appendicitis
- Surgical findings: mesenteric adenopathy, normal appendix
- Pathology report: appendicitis and reactive nodal hyperplasia

# False Positive LeuTech Scan



Anterior 61 minutes

- Phase 3 Patient C-3: 34 y.o. male
- LeuTech: Positive for appendicitis
- Surgery: Crohn’s Disease of Terminal Ileum with Obstruction

# LeuTech Imaging
## Observations

- Simple to perform
- Safe and does not require blood handling
- Easy to interpret
- Provides rapid diagnostic results in a difficult, equivocal patient population
- Improves overall patient management
- Surgeons and ER physicians continue to request LeuTech studies

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# LeuTech Clinical Experience

- Phase 1 - Biodistribution/Dosimetry N = 10
- Phase 2 - Appendicitis N = 56
- Phase 3 - Appendicitis N = 203
- Other
  - Investigator IND Pilot Studies N = 69*
  - Investigator IND HAMA Study N = 30*
  - European Study N = 17*
  - Phase 2 Osteomyelitis N = 24
  - Repeat-Dose HAMA Study N = 30

TOTAL N =439

*not conducted under Palatin IND

# Phase 1 Study

- Evaluated safety, biodistribution, pharmacokinetics and radiation dosimetry
- 10 healthy volunteers, single site
  - 6 female, 4 male
  - 20 to 46 years
- No adverse events reported
- No clinically significant changes in vital signs or clinical laboratory measurements related to LeuTech

# Phase 1 Study (cont'd)

- Radioactivity excreted primarily via urine
- 45% of radioactive injected dose is in the liver at 1 hour post-injection
- Highest radiation absorbed doses:
  - spleen (0.23 rad/mCi)
  - kidneys (0.19 rad/mCi)
  - liver (0.18 rad/mCi)
  - bladder wall (0.12 rad/mCi)
- Effective dose equivalent = 0.068 rem/mCi

# Equivocal Appendicitis Studies
## Phase 2 and Phase 3 Studies

- Phase 2 Study
  - 56 patients with equivocal appendicitis
  - 2 sites in U.S.
  - “gold standard” was final institutional diagnosis (surgery/pathology report or 1 month follow-up)
- Phase 3 Pivotal Study
  - 203 patients with equivocal appendicitis
  - multicenter - 10 sites in U.S.
  - “gold standard” was final institutional diagnosis (surgery/pathology report or 2-week follow-up)
- Similar study design for both studies

# Inclusion Criteria
## Phase 2 and Phase 3 Studies

- Males and females
- Pediatric, adult and geriatric patients
  - ≥ 8 years for Phase 2
  - ≥ 5 years for Phase 3
- RLQ pain and equivocal presentation of acute appendicitis
  - Absence of typical signs, symptoms or history

# Equivocal Signs and Symptoms

## Phase 2 and Phase 3 Studies

- Atypical history/symptoms
  - absence of periumbilical pain migrating to RLQ
  - no gradual onset of pain
  - no increasing intensity of pain over time
  - pain not aggravated by movement and coughing
- Atypical physical examination
  - absence of McBurney's point tenderness
  - absence of referred tenderness to RLQ with palpation in other quadrants
  - absence of abdominal muscular spasm with RLQ tenderness
- Temperature less than 101° F
- WBC count less than 10,500/$mm^3$

# Major Exclusion Criteria

## Phase 2 and Phase 3 Studies

- Phase 2
  - Pregnant and nursing women
- Phase 3
  - Pregnant and nursing women
  - Diagnosis of Pelvic Inflammatory Disease (PID)
  - Patients with 2 or more hospital admissions for abdominal pain of unknown etiology in past 6 months
  - Patients who had already undergone CT for work-up of current episode of RLQ abdominal pain

# Clinical Trial Design
## Phase 3 Study

- Primary Efficacy Indicators
  - Sensitivity and specificity of Blinded Readers' evaluations
  - Statistical evaluation:  95% one-sided Confidence Intervals

- Secondary Efficacy Indicators
  - Accuracy, PPV and NPV of Blinded Readers' evaluations
  - Site Investigator evaluations
  - Intended clinical management and likelihood of appendicitis

# LeuTech Dosage

## Phase 2 and Phase 3 Studies

- Adult Dose
  - 10 mCi - 20 mCi Tc 99m LeuTech (containing 75 - 125 µg anti-CD15 antibody)
- Pediatric Dose (5 - 17 years)
  - 0.21 mCi per kg body weight with maximum of 20 mCi

# Image Acquisition

## Phase 2 and Phase 3 Studies

- Imaging of lower abdomen with LFOV camera
  - low-energy, parallel-hole, high resolution collimator
  - photopeak at 140 keV ± 10%
- Dynamic image acquisition
  - immediately post-injection for ten 4-minute frames
- Static supine anterior, posterior, 20° - 25° RAO and LAO planar images
- Standing anterior image
- Additional images and SPECT imaging optional

# Image Evaluation

## Phase 2 and Phase 3 Studies

- Images read by site investigators and Blinded Readers
- Images read as “negative for infection” or “positive for infection”
  - no indeterminate reads
  - “positive for infection” scans classified as “appendicitis” or “other infection”
- Time of first positive image was recorded in Phase 3

# Blinded Reader Evaluations

## Phase 2 and Phase 3 Studies

- Managed by independent core laboratory
- 3 Blinded Readers (not otherwise participating in study)
- No clinical history or symptoms provided (Phase 3)
- Demographic information provided
  - age, sex, height, weight
- Images presented on computer monitors
  - dynamic images evaluated as endless loop cine display

# Patient Management Plan

## Phase 2 and Phase 3 Studies

- Surgeons completed questionnaires before imaging, indicating:
  - likelihood of appendicitis on a five point scale
  - treatment plan
    - surgery
    - admit for observation
    - send home
- Same questionnaire was completed after imaging, prior to further treatment or testing.

# Demographics
## Phase 2 Study

- 56 patients enrolled at 2 sites
  - 31 female, 25 male
  - 9 to 77 years (15 patients < 18 years)
  - 28 (50%) acute appendicitis
    - 9 perforated appendix
  - 28 (50%) no appendicitis
    - 7 “other infection”

# Efficacy Results
## Phase 2 Study

| | Blinded Read* | Site Investigator |
|---|---|---|
| Accuracy | 79 | 88 |
| Sensitivity | 89 | 96 |
| Specificity | 68 | 79 |
| PPV | 74 | 82 |
| NPV | 86 | 96 |
| Total Patients | 56 | 56 |
| Positive | 28 | 28 |
| Negative | 28 | 28 |

*Aggregate results

# Demographics
## Phase 3 Study

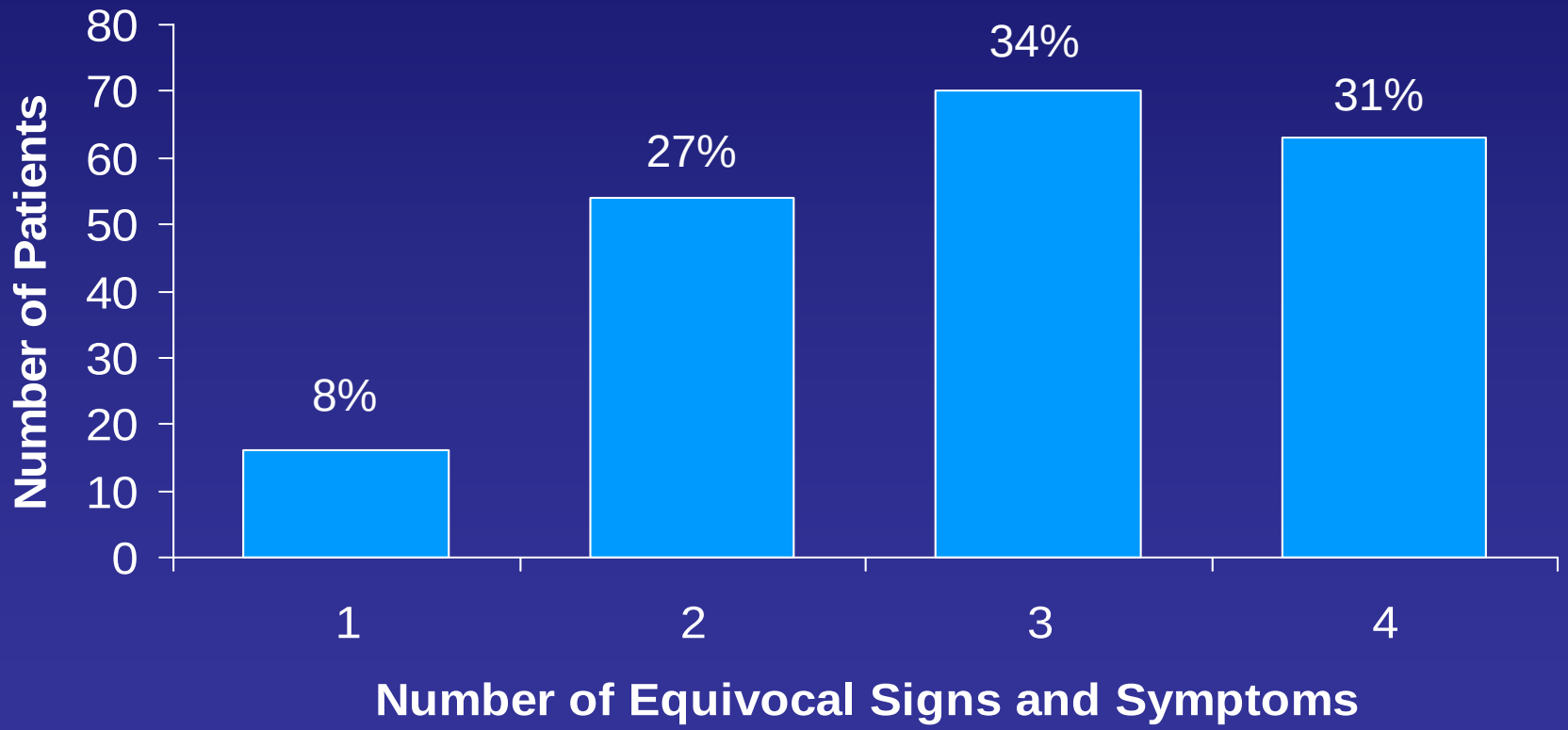
- 203 patients enrolled at 10 sites
  - 200 evaluable patients
- Six sites enrolled between 19 and 39 patients
- 60% female, 40% male
- 5 to 86 years (49 patients < 18 yrs)
- 59 (30%) acute appendicitis
  - 13 perforated appendix
- 141 (70%) no appendicitis
  - 23 “other infections”

# Equivocal Population
## Phase 3 Study

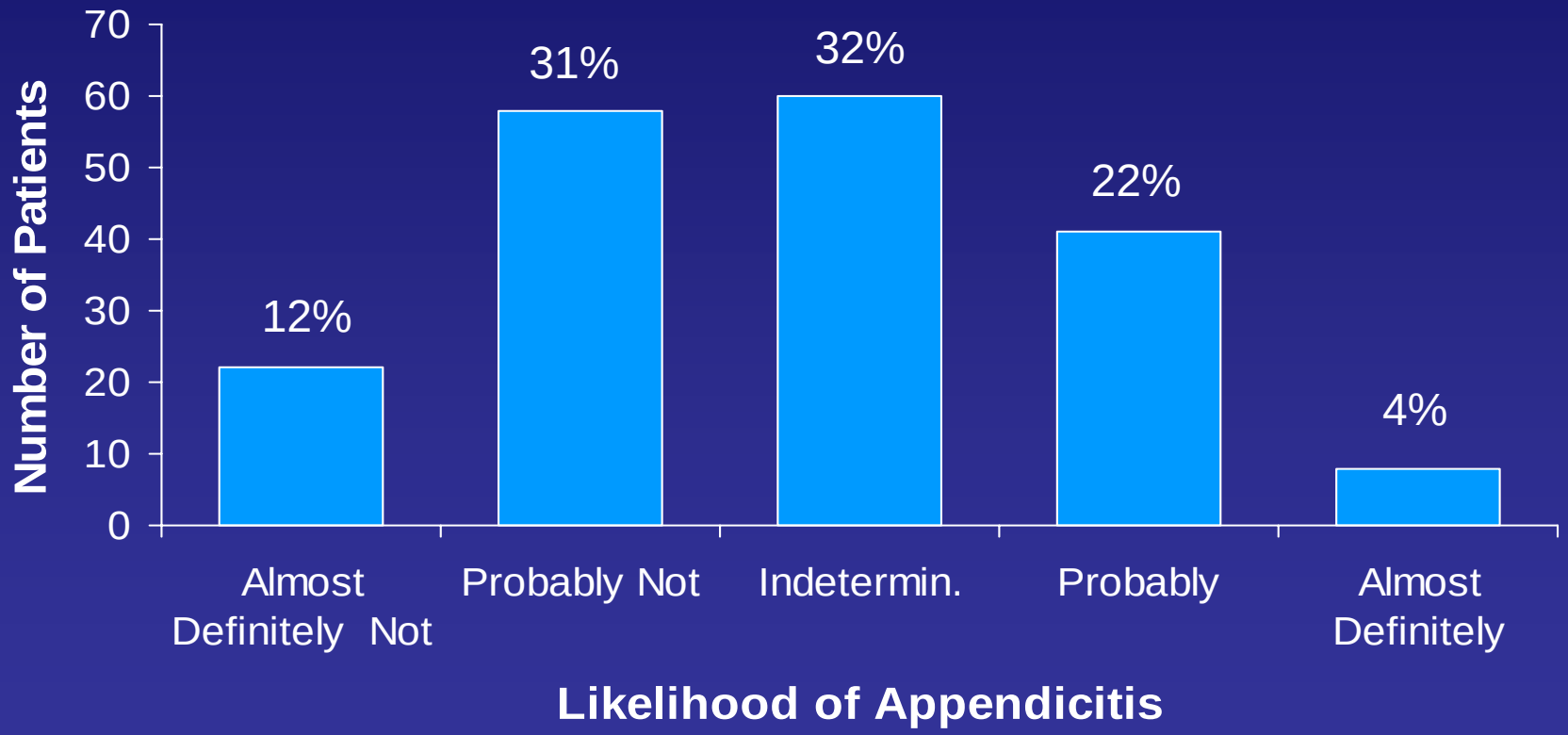
- Absence of classic signs and symptoms
- Surgeons' assessment of the likelihood of appendicitis
- Prevalence of "admit for observation" as surgeons' intended management plan

# Equivocal Presentation of Appendicitis
## Phase 3 Study

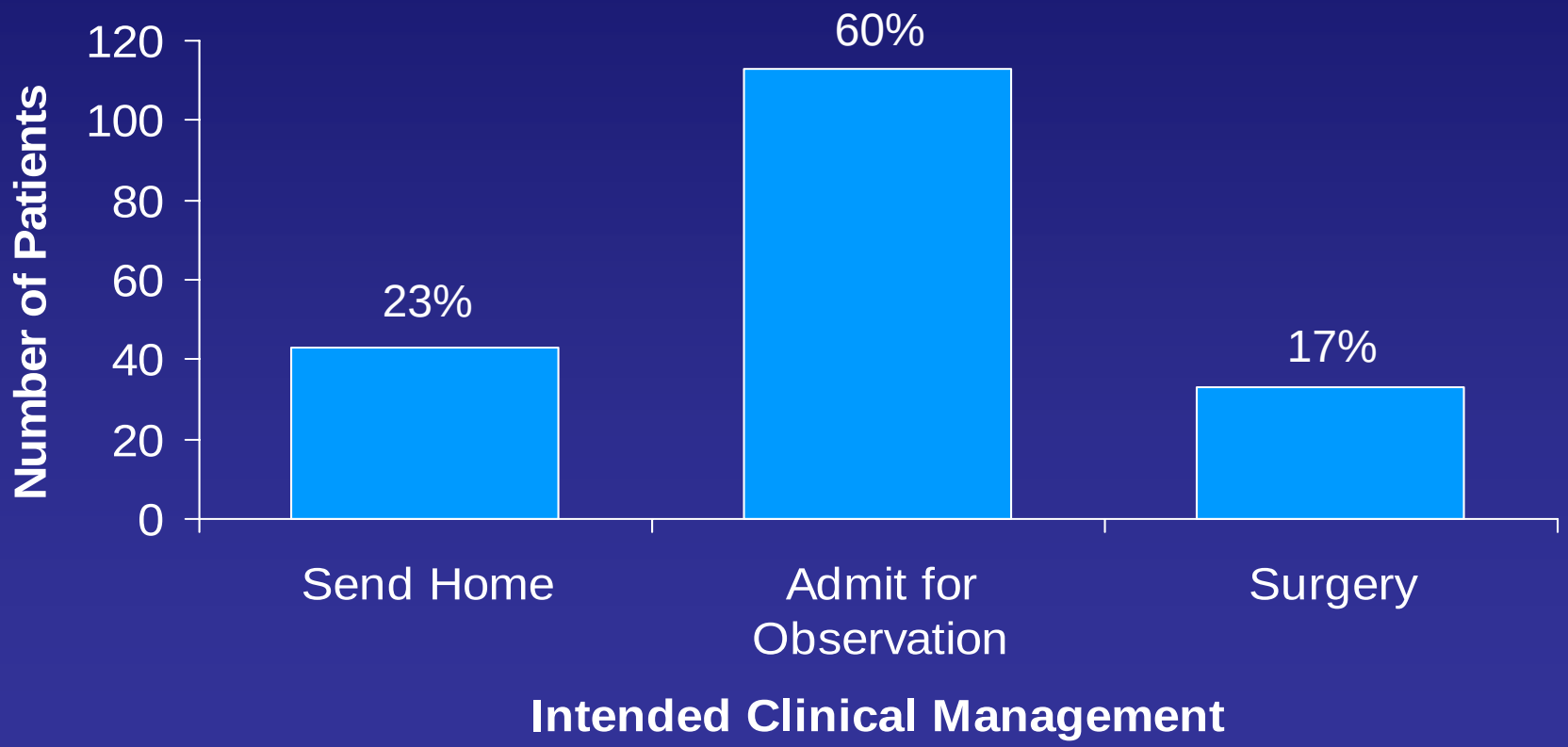
- 92% with ≥ 2 equivocal signs/symptoms
- 65% with ≥ 3 equivocal signs/symptoms



# Pre-Scan Likelihood of Appendicitis
## Phase 3 Study

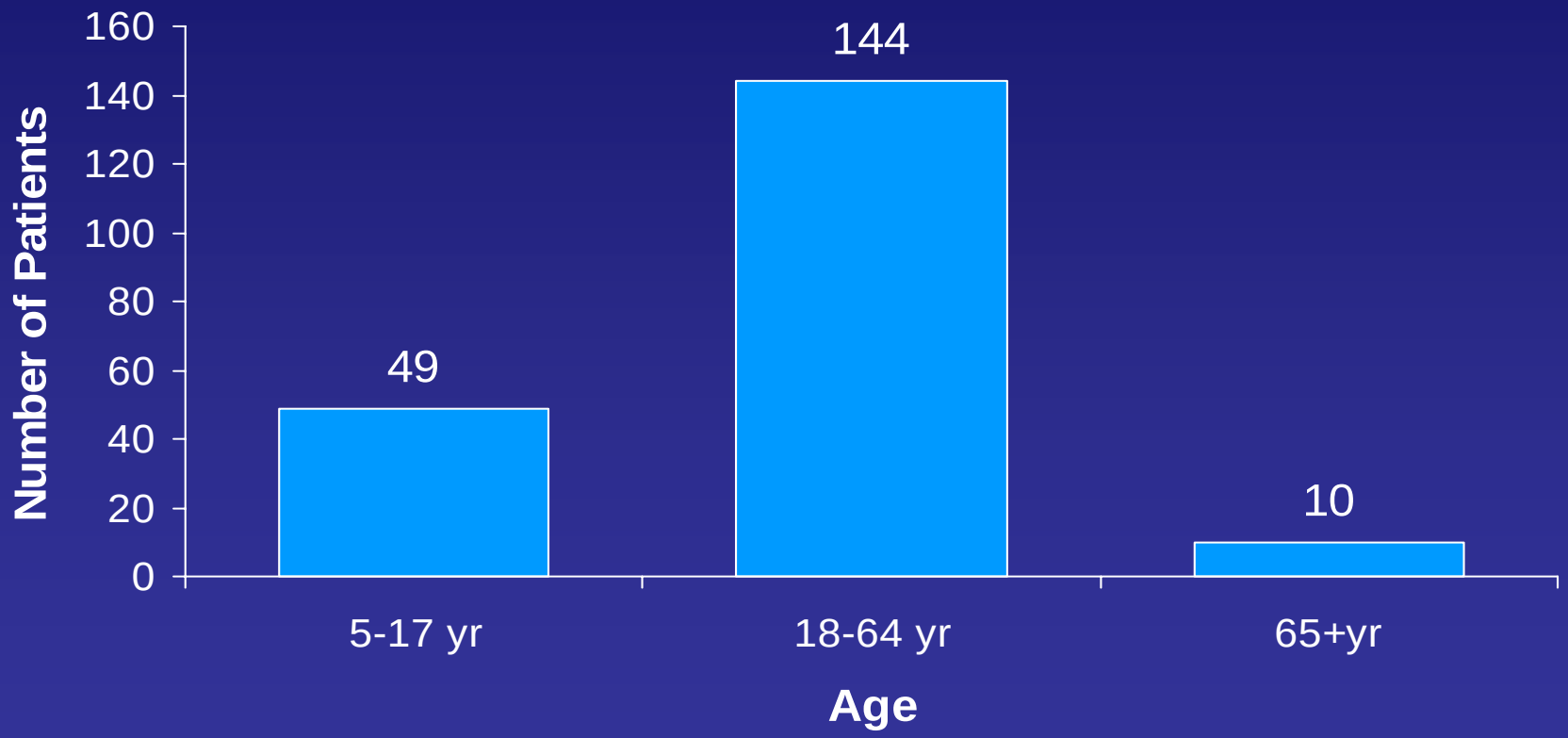


# Pre-Scan Intended Clinical Management
## Phase 3 Study



# Age Distribution

## Phase 3 Study



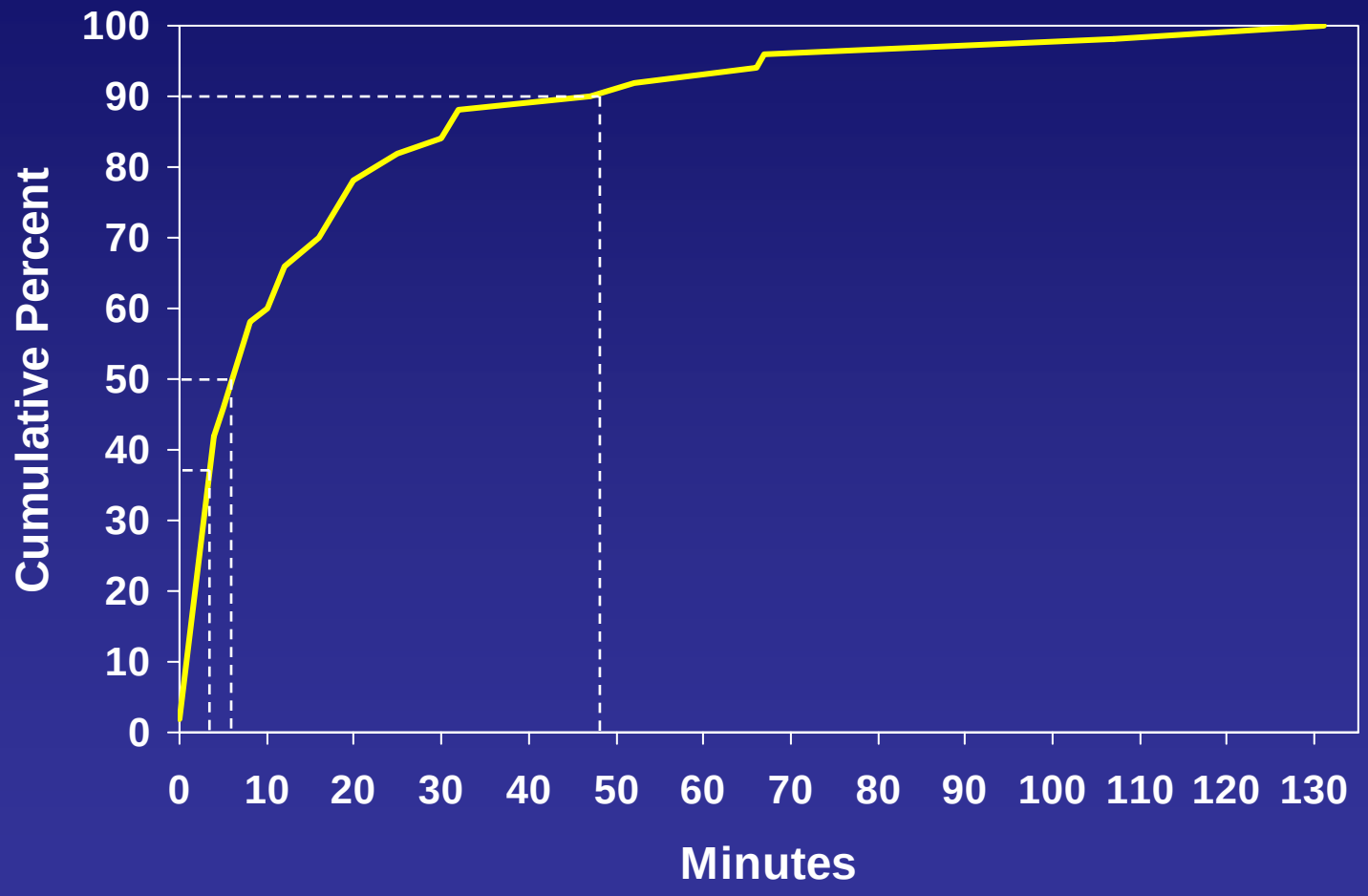
# LeuTech Imaging

## Phase 3 Study

- Simple planar imaging
  - standard high resolution collimator
- SPECT not required
  - optional in protocol
  - only 9 of 203 patients had SPECT (8 at one site)
  - SPECT images not included in Blinded Read

# Time to First Positive Image

## Phase 3 Patients with Appendicitis



# Efficacy Results
## Phase 3 Study

| | Blinded Read* | Site Investigator |
|---|---|---|
| Accuracy | 88 | 87 |
| Sensitivity | 75 | 91 |
| Specificity | 93 | 86 |
| PPV | 82 | 73 |
| NPV | 90 | 96 |
| Total Patients | 200 | 182 |
| Positive | 59 | 54 |
| Negative | 141 | 128 |

*Aggregate results, Concordance 88% to 90%, Kappa 0.54 to 0.55

# Likelihood Ratios
## Phase 3 Study

| | LR(+) | LR(-) |
|---|---|---|
| Blinded Reader 1 | 6.75 | 0.21 |
| Blinded Reader 2 | 6.66 | 0.38 |
| Blinded Reader 3 | 13.44 | 0.25 |
| Aggregate | 10.52 | 0.27 |
| Site Investigators | 6.45 | 0.11 |

- Odds that reader correctly diagnosed appendicitis with LeuTech were 6 to 13 times greater than the pre-test odds of appendicitis.
- Odds that reader missed a diagnosis of appendicitis with LeuTech was reduced 1/9 to 1/3 times the pre-test odds of appendicitis.

# Blinded Read Results*
## Phase 2 and Phase 3 Studies

| | Phase 2 | Phase 3 |
|---|---|---|
| Accuracy | 79 | 88 |
| Sensitivity | 89 | 75 |
| Specificity | 68 | 93 |
| PPV | 74 | 82 |
| NPV | 86 | 90 |
| Total Patients | 56 | 200 |
| Positive | 28 | 59 |
| Negative | 28 | 141 |

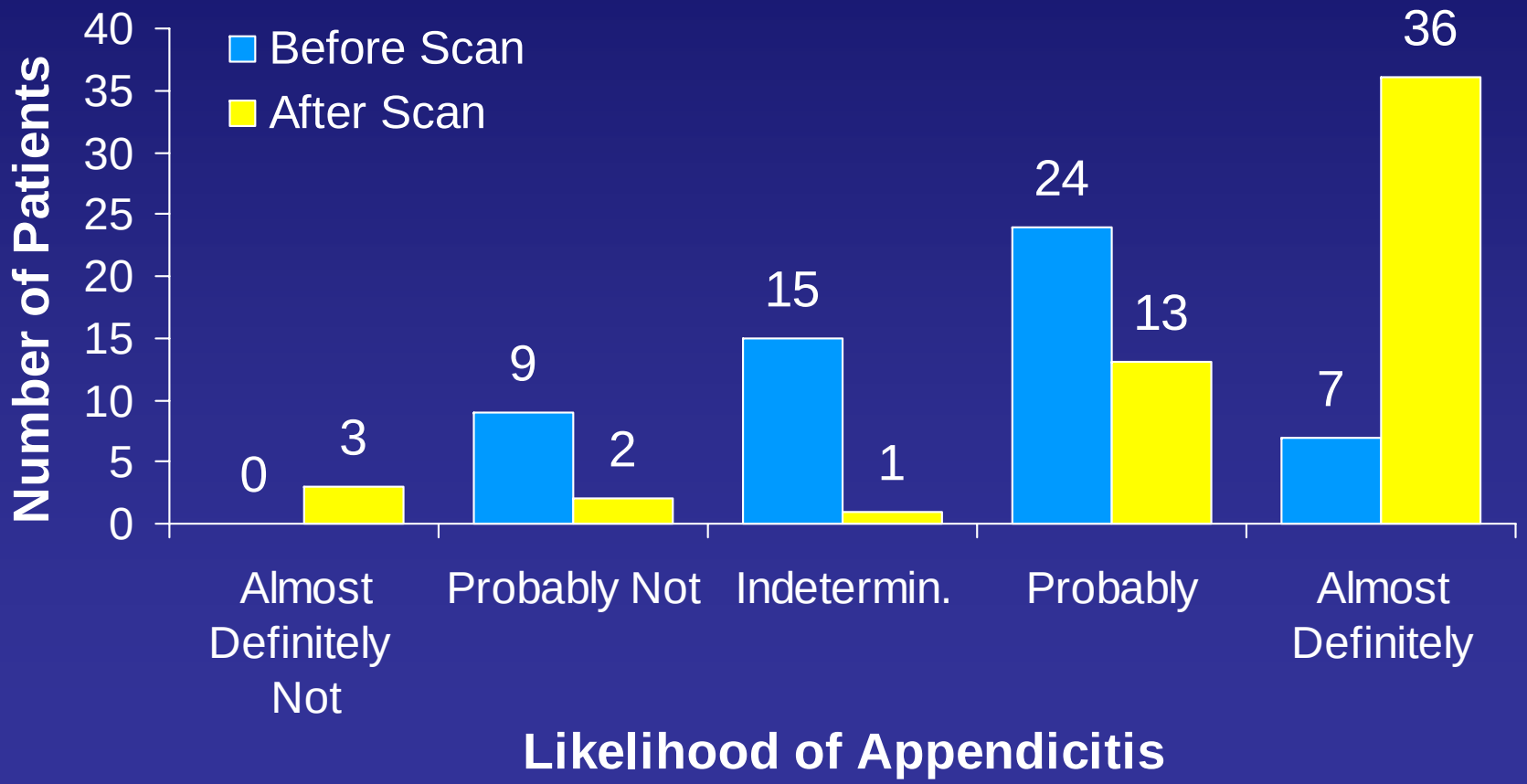
*Aggregate results

# Site Investigator Results
## Phase 2 and Phase 3 Studies

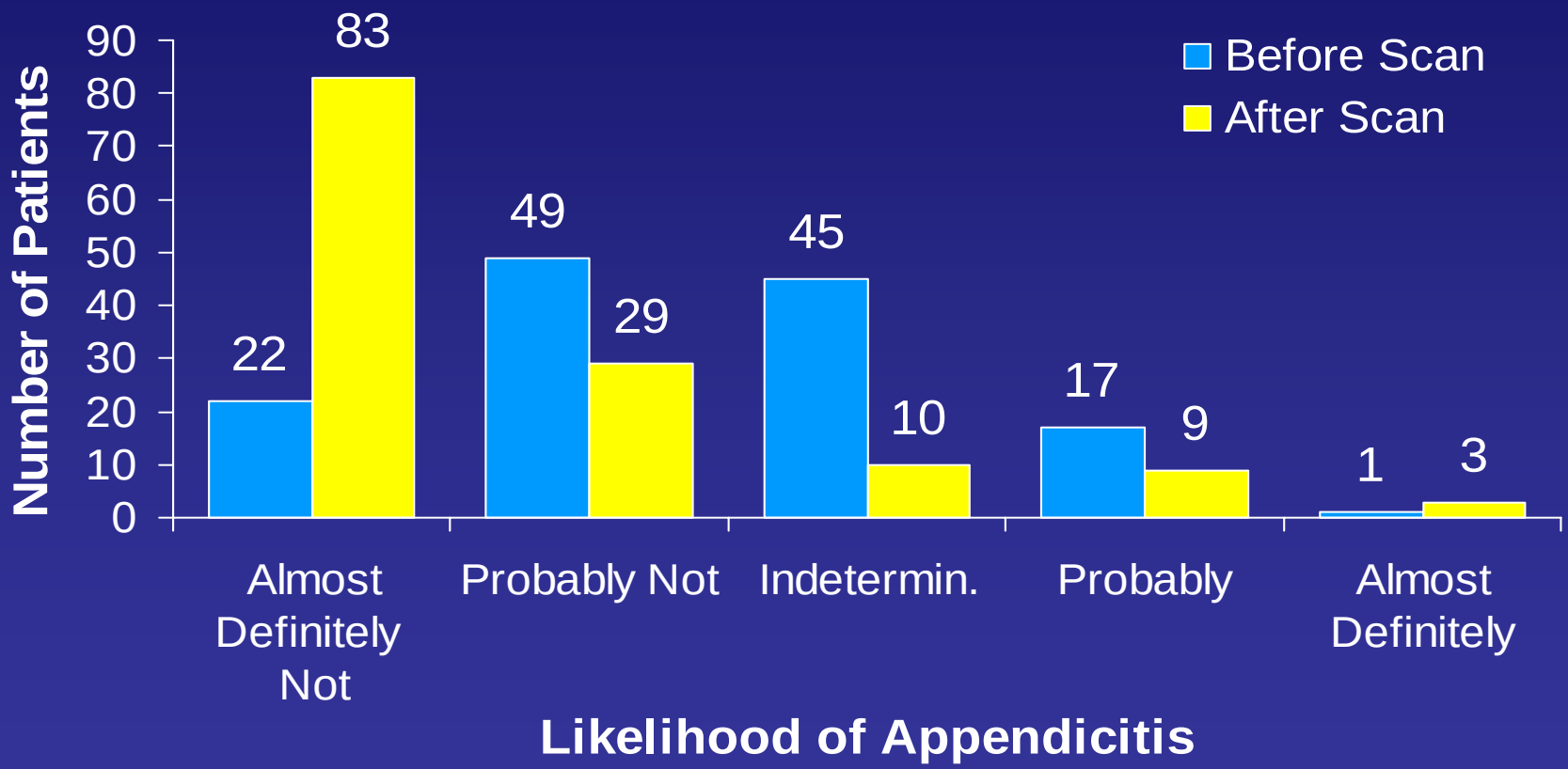
| | Phase 2 | Phase 3 |
|---|---|---|
| Accuracy | 88 | 87 |
| Sensitivity | 96 | 91 |
| Specificity | 79 | 86 |
| PPV | 82 | 73 |
| NPV | 96 | 96 |
| Total Patients | 56 | 182 |
| Positive | 28 | 54 |
| Negative | 28 | 128 |

# Likelihood of Appendicitis

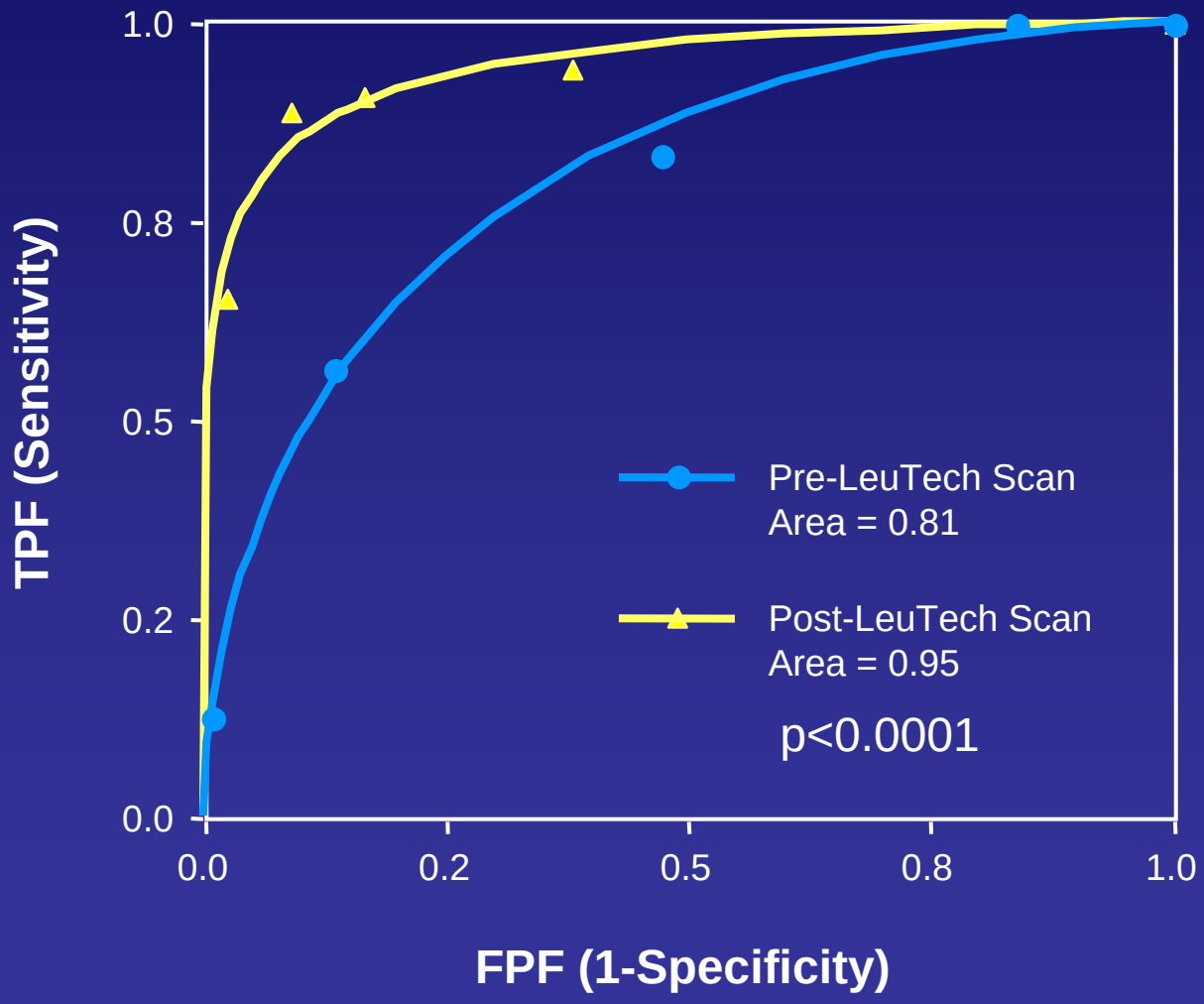
## Phase 3 Patients with Appendicitis



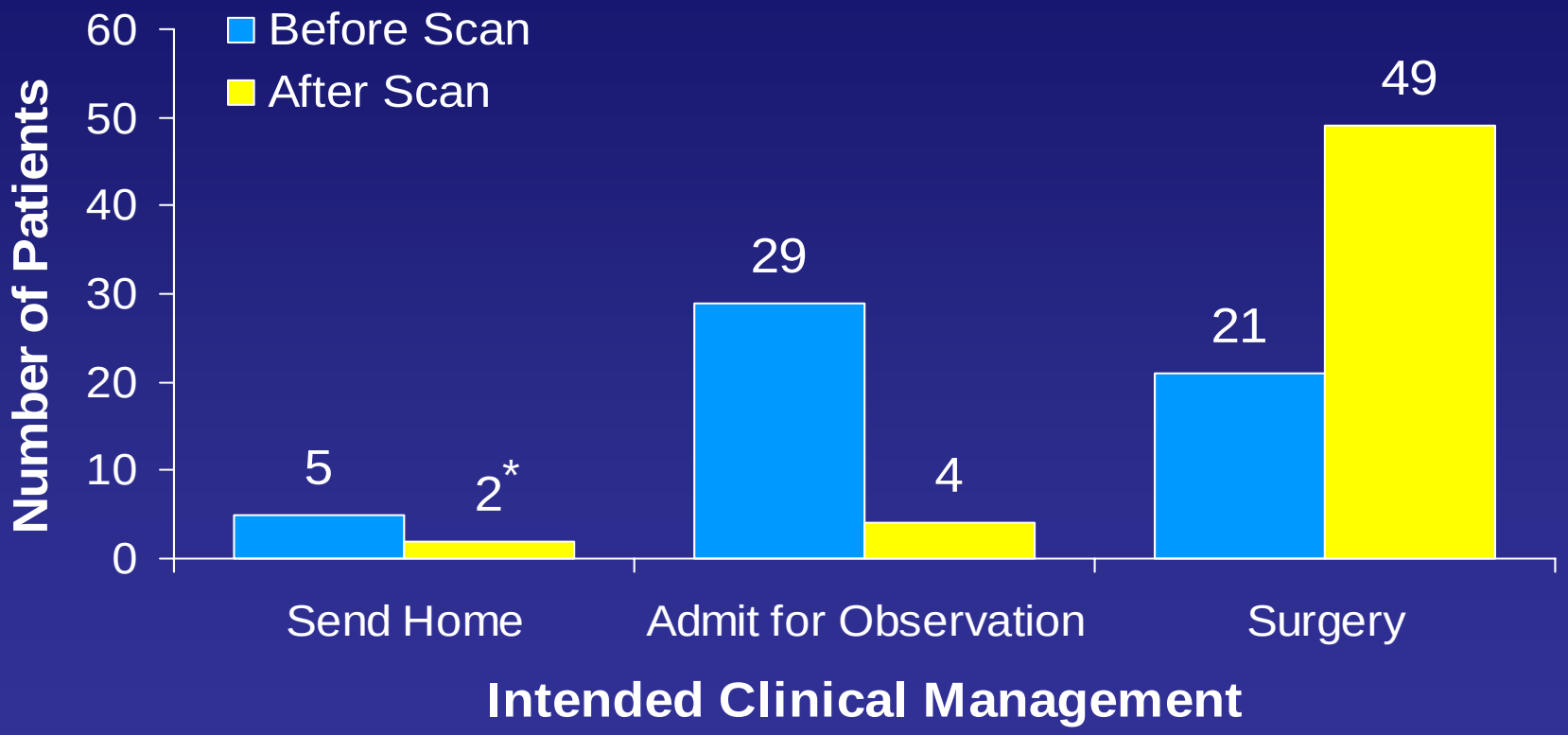
# Likelihood of Appendicitis
## Phase 3 Patients without Appendicitis



# ROC Curve Analysis
## Likelihood of Appendicitis – Phase 3

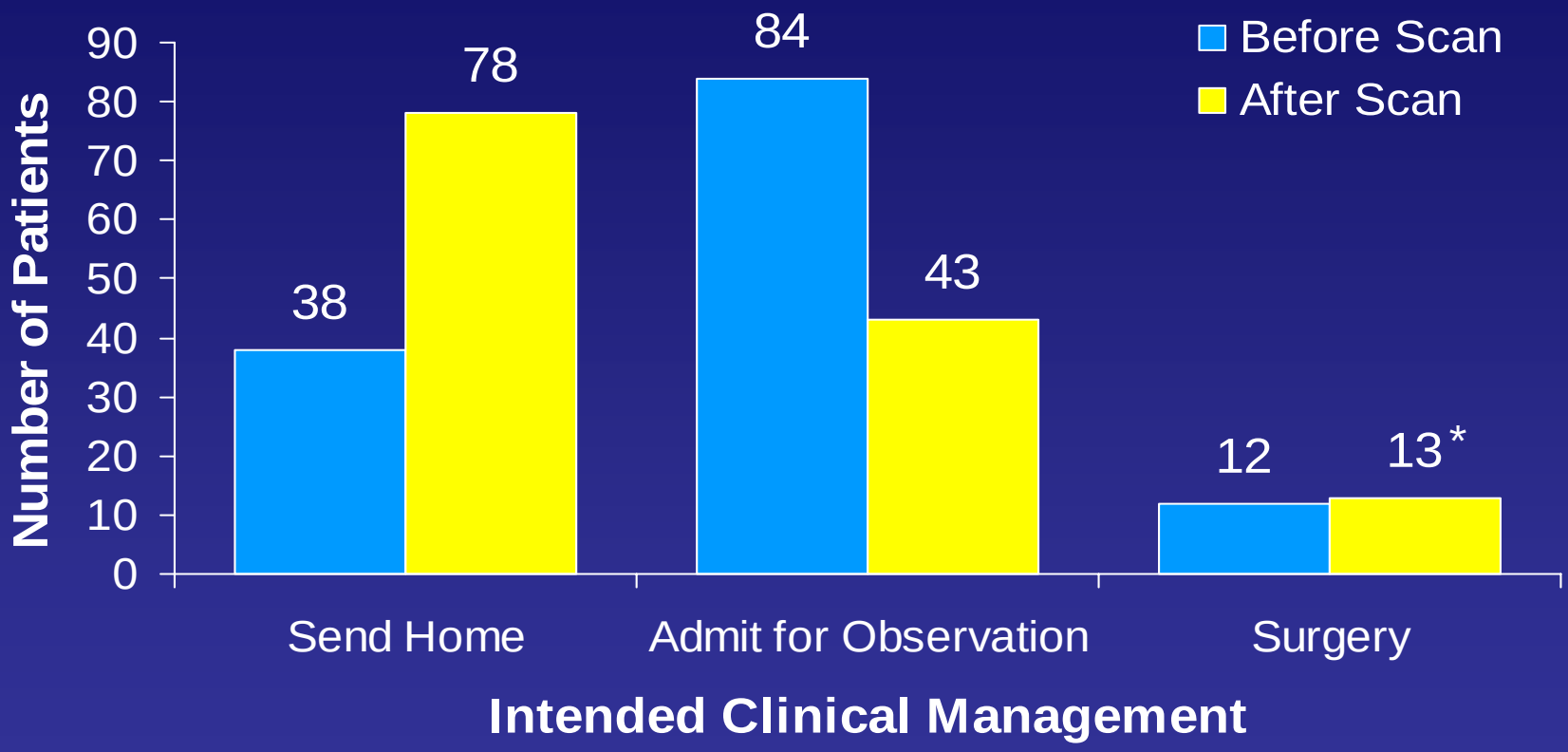


# Intended Clinical Management
## Phase 3 Patients with Appendicitis




*One patient had a positive LeuTech scan

# Intended Clinical Management
## Phase 3 Patients without Appendicitis




*4 of 13 patients had other disease requiring surgery

# Intended Clinical Management Plans
## Phase 3 Study

- LeuTech favorably impacts patient management
  - 74 of 189 patients (39%) had favorable shifts
  - 25 patients with appendicitis shifted from ‘admit for observation’ to ‘surgery’
  - 0 patients with appendicitis shifted away from ‘surgery’
  - 39 patients without appendicitis shifted from ‘admit for observation’ to ‘send home’

- Difference between pre- and post-scan management was statistically significant ($p<0.00001$)

# Overall LeuTech Safety Data

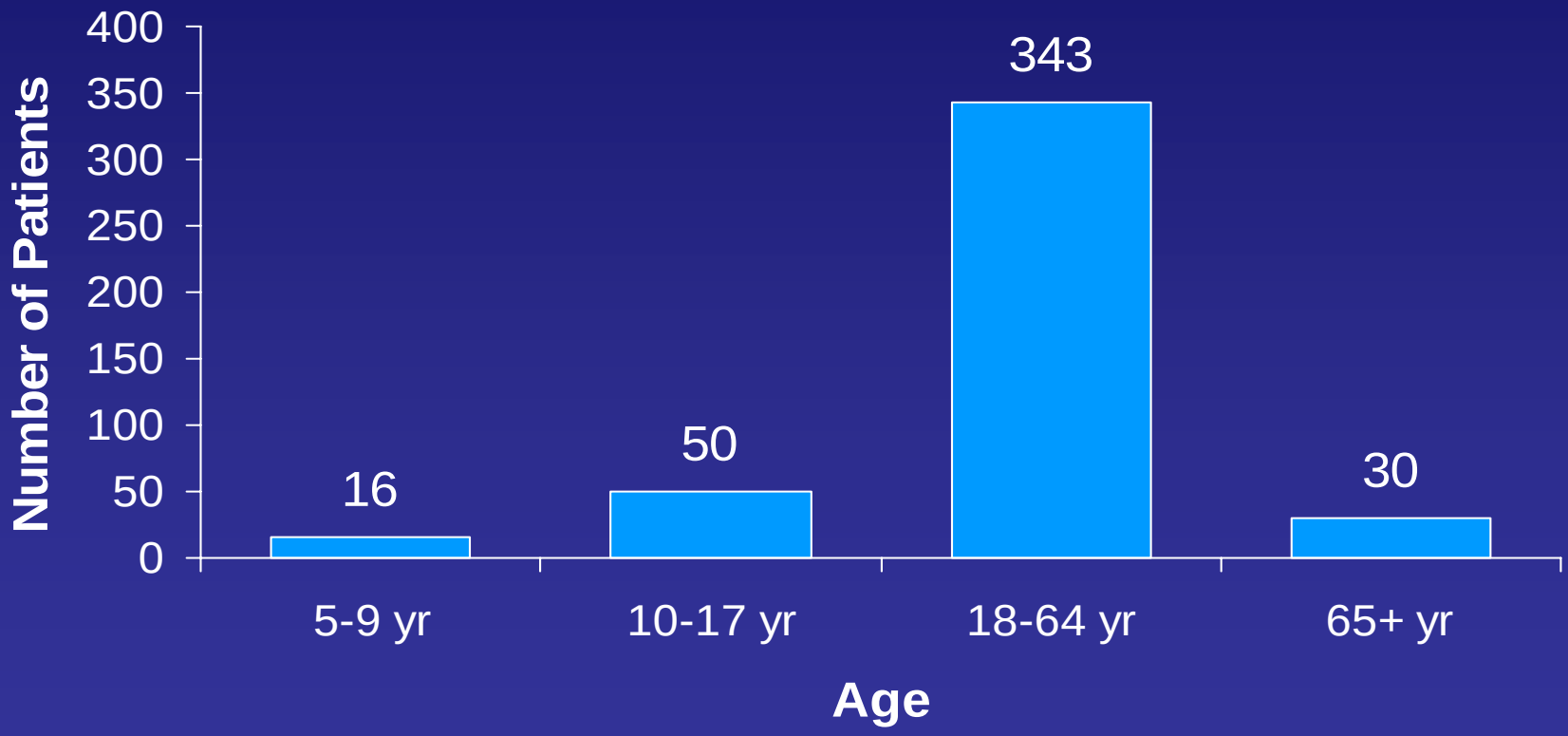
- Safety measurements included
  - Adverse Events
  - Clinical Laboratory Measurements
  - Vital Signs
  - HAMA Measurements
- Overall summary of safety for 439 subjects
  - includes all subjects injected (Palatin IND studies and other studies)
  - 393 subjects included in original BLA filing
  - 46 subjects summarized in 120-Day Safety Update to BLA

# Overall Safety Population

## All Subjects

- 439 subjects
- 202 males, 237 females
- Mean age 34.1 years (5.2 yr to 91.4 yr)
- Mean anti-CD15 IgM antibody dose 120.1 μg
- Mean radioactive dose 14.5 mCi

# Age Distribution
## All Subjects



# Adverse Events
## Overall Incidence (N = 439)

- 30 subjects experienced 39 AEs
- No serious adverse events
- Single “moderate-severe” AE (injection site pain)

# Adverse Events
## Overall Incidence (N = 439)

- Vasodilatation (flushing), 11 subjects (2.5%)
- Dyspnea, 4 subjects (0.9%)
- All others < 0.7%
  - headache
  - pain (injection site, abdomen, chest)
  - asthenia
  - malaise
  - syncope
  - diarrhea
  - ecchymosis
  - joint disorder
  - dizziness
  - paresthesia
  - pharyngitis
  - rhinitis

# Adverse Events
## Drug Related

- 20 AEs in 14 subjects classified as “possibly or probably related” to LeuTech
  - headache 1 ( 0.2%)
  - injection site reaction 1 (0.2%)
  - chest pain 1 (0.2%)
  - injection site pain 1 (0.2%)
  - vasodilatation/flushing 11 (2.5%)
  - ecchymosis 1 (0.2%)
  - dizziness 1 (0.2%)
  - paresthesia 1 (0.2%)
  - dyspnea 2 (0.5%)

# Clinical Laboratory Measurements

- Clinical laboratory measurements obtained in 4 of 8 clinical trials (N = 242 subjects)
- Investigators assessed clinical significance of changes in clinical laboratory measurements
- 7 clinically significant changes in 4 subjects (1.7%)
  - lab error in one subject
  - disease-related in 2 patients
  - possibly related to LeuTech in one subject
    elevated LDH and AST resolved without treatment

# Vital Signs

- Vital signs measured in 6 of 8 clinical trials (N = 383)
  - pulse rate
  - blood pressure
  - oral body temperature
- Mean vital sign changes from baseline
  - several statistically significant changes noted
  - mean changes were very small in magnitude, with no clinical importance.

# Vital Signs (cont'd)

- Clinically significant changes defined in protocol
  - systolic BP > 35 mm Hg
  - diastolic BP > 25 mm Hg
  - pulse rate > 20 beats per minute
- Clinically significant changes noted in 20 subjects
  - decrease in pulse in 7 subjects (1.8%)
  - increase in pulse in 5 subjects (1.3%)
  - decrease in BP in 3 subjects (0.8%)
  - increase in BP in 5 subjects (1.3%)
- No vital sign changes attributed to LeuTech

# HAMA Response
## Single Injection

- HAMA response to a single injection of LeuTech was evaluated in 3 of 8 studies (N = 54)
  - 30 normal volunteers (HAMA study)
  - 20 patients (Phase 3 appendicitis study)
  - 4 patients (Investigator IND study)
- HAMA levels measured at baseline and 3-4 weeks post-injection
- No positive responses in any of the 54 subjects

# Summary of Efficacy

- LeuTech was found to be effective in two clinical trials for diagnosing and ruling out appendicitis.
- Results in pivotal Phase 3 trial corroborated earlier Phase 2 trial.
- Accuracy of blinded readers (83% - 89%) was consistent with site investigators (87%).
- LeuTech scan had a favorable impact on intended clinical management.

# Summary of Safety

- No serious side effects.
- Only 30 of 439 subjects experienced AEs (39 events).
  - No serious AEs
  - 20 AEs in 14 subjects considered possibly related to LeuTech
  - Vasodilatation (flushing) reported by 11 (2.5%) subjects
  - No other AEs with incidence over 1%
- Minimal incidence of clinically significant changes in vital signs and clinical laboratory measurements
- No HAMA response following single injection

# Conclusion

LeuTech has been shown to be a safe and effective diagnostic agent for diagnosing and ruling out appendicitis in patients presenting with equivocal signs and symptoms.

# LeuTech
## MIDAC Meeting Agenda

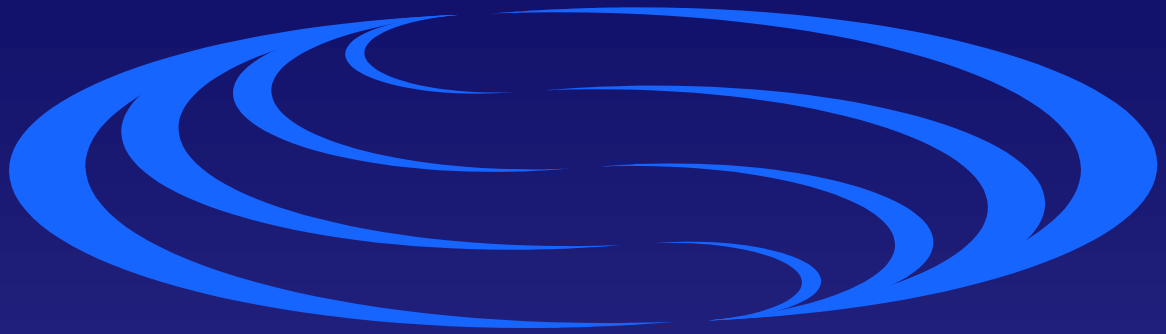
| | |
|---|---|
| Introduction | C. Putnam |
| Description of LeuTech | T. Smith, Ph.D. |
| Equivocal Appendicitis | E. Rypins, M.D. |
| Imaging Techniques and Interpretation | S. Kipper, M.D. |
| Clinical Development Program | K. McElvany, Ph.D. |
| Conclusion | C. Putnam |

# LeuTech

- Accurate (87%) in patients presenting with equivocal signs and symptoms of appendicitis
- Useful to rule out appendicitis (NPV 96%)
- Safe - no significant adverse events in 439 patients
- Improves patient management by facilitating earlier surgery in patients with appendicitis and earlier discharge in patients without appendicitis.

# LeuTech - Proposed Indication

Scintigraphy with Technetium Tc 99m Anti-CD15 Antibody is indicated for the diagnosis of appendicitis in patients with equivocal signs and symptoms. It is useful to rule out appendicitis in patients presenting with equivocal diagnostic evidence.



# PALATIN

## TECHNOLOGIES, INC.

CP013.01