FDA Medical Imaging Drugs Advisory Committee

July 10, 2000

BLA 99-1407
LeuTech®

Palatin Technologies, Inc.
## Palatin Presenters

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charles Putnam</td>
<td>Chief Operating Officer</td>
<td>Palatin Technologies, Inc.</td>
</tr>
<tr>
<td>Terry Smith, Ph.D.</td>
<td>Executive Director of Product Development</td>
<td>Palatin Technologies, Inc.</td>
</tr>
<tr>
<td>Eric Rypins, M.D.</td>
<td>Department of Surgery</td>
<td>Tri-City Medical Center</td>
</tr>
<tr>
<td>Samuel Kipper, M.D.</td>
<td>Director of Nuclear Medicine</td>
<td>Tri-City Medical Center</td>
</tr>
<tr>
<td>Karen McElvany, Ph.D.</td>
<td>Director of Clinical Affairs</td>
<td>Certus International, Inc.</td>
</tr>
</tbody>
</table>
## Additional Palatin Consultants

- **Robert Carretta, M.D.**  
  Sutter-Roseville Medical Center  
  Roseville, California

- **Christopher Palestro, M.D.**  
  Long Island Jewish Medical Center  
  New Hyde Park, New York

- **Mathew Thakur, Ph.D.**  
  Thomas Jefferson University  
  Philadelphia, Pennsylvania

- **M.B. Khazaei, Ph.D.**  
  Univ. of Alabama  
  Wallace Tumor Institute  
  Birmingham, Alabama

- **Kathleen Madsen, Ph.D.**  
  Certus International, Inc.  
  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
- 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
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
<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>C. Putnam</td>
</tr>
<tr>
<td>Description of LeuTech</td>
<td>T. Smith, Ph.D.</td>
</tr>
<tr>
<td>Equivocal Appendicitis</td>
<td>E. Rypins, M.D.</td>
</tr>
<tr>
<td>Imaging Techniques and Interpretation</td>
<td>S. Kipper, M.D.</td>
</tr>
<tr>
<td>Clinical Development Program</td>
<td>K. McElvany, Ph.D.</td>
</tr>
<tr>
<td>Conclusion</td>
<td>C. Putnam</td>
</tr>
</tbody>
</table>
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 \((K_d = 10^{-11} \text{ M})\)
  - Abundant binding sites \((\sim 5.1 \times 10^5 \text{ antigens per PMN})\)

- 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%
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
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
LeuTech
MIDAC Meeting Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>C. Putnam</td>
</tr>
<tr>
<td>Description of LeuTech</td>
<td>T. Smith, Ph.D.</td>
</tr>
<tr>
<td>Equivocal Appendicitis</td>
<td>E. Rypins, M.D.</td>
</tr>
<tr>
<td>Imaging Techniques and Interpretation</td>
<td>S. Kipper, M.D.</td>
</tr>
<tr>
<td>Clinical Development Program</td>
<td>K. McElvany, Ph.D.</td>
</tr>
<tr>
<td>Conclusion</td>
<td>C. Putnam</td>
</tr>
</tbody>
</table>
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

SK002.02
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

Phase 3 Patient A-03: 8 y.o. female
Typical Static Image Sequence
Negative Scan

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

Anterior 59 min  
Posterior 59 min  
Right Anterior Oblique 67 min  
Left Anterior Oblique 76 min

SK005.02
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

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

- 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

- 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

- 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
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 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
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
  - $\geq 8$ years for Phase 2
  - $\geq 5$ 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/mm³
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.
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

<table>
<thead>
<tr>
<th></th>
<th>Blinded Read*</th>
<th>Site Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>79</td>
<td>88</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>89</td>
<td>96</td>
</tr>
<tr>
<td>Specificity</td>
<td>68</td>
<td>79</td>
</tr>
<tr>
<td>PPV</td>
<td>74</td>
<td>82</td>
</tr>
<tr>
<td>NPV</td>
<td>86</td>
<td>96</td>
</tr>
<tr>
<td>Total Patients</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Positive</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Negative</td>
<td>28</td>
<td>28</td>
</tr>
</tbody>
</table>

*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

![Bar chart showing the likelihood of appendicitis.]

- Almost Definitely: 12%
- Probably Not: 31%
- Indeterminant: 32%
- Probably: 22%
- Almost Definitely: 4%
Pre-Scan Intended Clinical Management
Phase 3 Study

Intended Clinical Management

Number of Patients

Send Home: 23%
Admit for Observation: 60%
Surgery: 17%
Age Distribution
Phase 3 Study

Number of Patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-17 yr</td>
<td>49</td>
</tr>
<tr>
<td>18-64 yr</td>
<td>144</td>
</tr>
<tr>
<td>65+yr</td>
<td>10</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Blinded Read*</th>
<th>Site Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong></td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>75</td>
<td>91</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>82</td>
<td>73</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td><strong>Total Patients</strong></td>
<td><strong>200</strong></td>
<td><strong>182</strong></td>
</tr>
<tr>
<td>Positive</td>
<td>59</td>
<td>54</td>
</tr>
<tr>
<td>Negative</td>
<td>141</td>
<td>128</td>
</tr>
</tbody>
</table>

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

**Phase 3 Study**

<table>
<thead>
<tr>
<th></th>
<th>LR(+)</th>
<th>LR(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinded Reader 1</td>
<td>6.75</td>
<td>0.21</td>
</tr>
<tr>
<td>Blinded Reader 2</td>
<td>6.66</td>
<td>0.38</td>
</tr>
<tr>
<td>Blinded Reader 3</td>
<td>13.44</td>
<td>0.25</td>
</tr>
<tr>
<td>Aggregate</td>
<td>10.52</td>
<td>0.27</td>
</tr>
<tr>
<td>Site Investigators</td>
<td>6.45</td>
<td>0.11</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th>Metric</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>79</td>
<td>88</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>89</td>
<td>75</td>
</tr>
<tr>
<td>Specificity</td>
<td>68</td>
<td>93</td>
</tr>
<tr>
<td>PPV</td>
<td>74</td>
<td>82</td>
</tr>
<tr>
<td>NPV</td>
<td>86</td>
<td>90</td>
</tr>
<tr>
<td>Total Patients</td>
<td>56</td>
<td>200</td>
</tr>
<tr>
<td>Positive</td>
<td>28</td>
<td>59</td>
</tr>
<tr>
<td>Negative</td>
<td>28</td>
<td>141</td>
</tr>
</tbody>
</table>

*Aggregate results
## Site Investigator Results
### Phase 2 and Phase 3 Studies

<table>
<thead>
<tr>
<th></th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong></td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>79</td>
<td>86</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>82</td>
<td>73</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td><strong>Total Patients</strong></td>
<td>56</td>
<td>182</td>
</tr>
<tr>
<td><strong>Positive</strong></td>
<td>28</td>
<td>54</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>28</td>
<td>128</td>
</tr>
</tbody>
</table>
Likelihood of Appendicitis
Phase 3 Patients with Appendicitis

![Bar chart showing the likelihood of appendicitis before and after a scan.](chart.png)

- **Almost Definitely Not**
  - Before Scan: 0
  - After Scan: 3

- **Probably Not**
  - Before Scan: 9
  - After Scan: 2

- **Indetermin.**
  - Before Scan: 15
  - After Scan: 1

- **Probably**
  - Before Scan: 24
  - After Scan: 13

- **Almost Definitely**
  - Before Scan: 7
  - After Scan: 36
Likelihood of Appendicitis
Phase 3 Patients without Appendicitis

Number of Patients

- Almost Definitely Not
- Probably Not
- Indetermin.
- Probably
- Almost Definitely

Before Scan
After Scan

Likelihood of Appendicitis

KM028.02
ROC Curve Analysis
Likelihood of Appendicitis – Phase 3

Post-LeuTech Scan
Area = 0.95

Pre-LeuTech Scan
Area = 0.81

p < 0.0001

TPF (Sensitivity) vs. FPF (1-Specificity)
Intended Clinical Management
Phase 3 Patients with Appendicitis

- Before Scan
- After Scan

<table>
<thead>
<tr>
<th>Intended Clinical Management</th>
<th>Before Scan</th>
<th>After Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Send Home</td>
<td>5</td>
<td>2*</td>
</tr>
<tr>
<td>Admit for Observation</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Surgery</td>
<td>21</td>
<td>49</td>
</tr>
</tbody>
</table>

*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
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
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.
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.