FDA Briefing Document:

Medical Imaging Device Advisory Committee (MIDAC)
July 10, 2000

LeuTech®

BLA # 99-1407

Section I
A. Introduction

Purpose: This briefing document presents data from clinical studies of LeuTech as submitted in the BLA application from Palatin and an analysis of these data in order for the Medical Imaging Device Advisory Committee to render advice and comments on the safety and efficacy of this product

Product: A Sodium Pertechnetate Tc 99m labeled Murine Monoclonal Antibody that binds to neutrophil CD 15 antigens.

Proposed Indication: Scintigraphy with LeuTech is indicated for the diagnosis of appendicitis in patients with equivocal signs and symptoms.

LeuTech utilizes a radiolabelled monoclonal mouse antibody, which binds to CD15 found on polymorphonuclear leukocytes (PMNL). PMNL function appears to be maintained during this binding. Initial development hypothesized that this product could detect inflammatory conditions where there would be an accumulation of PMNLs. This could be useful in the diagnosis of appendicitis and differentiating that from non-inflammatory etiologies of right lower quadrant (RLQ) pain and inflammatory conditions that were located at a different site in the abdomen.

Although the diagnosis of appendicitis is usually straightforward, there are many cases that are atypical and require further testing beyond the history and physical exam. Initial testing involves laboratory evaluations, most commonly a complete blood count (CBC) and a urinalysis. If the diagnosis is still in question, radiological evaluation is usually pursued. Anatomical imaging such as abdominal CT scans have been useful in aiding in making the diagnosis of appendicitis and also identifying other etiologies for the presenting symptoms. LeuTech provides a different approach by nuclear medicine imaging of WBC and thereby identifying sites of inflammation, specifically the appendix.

This review will exam the data available from the sponsor with regard to the safety and efficacy of this product in the diagnosis of appendicitis in patients presenting with atypical signs and symptoms. It will focus also on specific subgroups including but not limited to pediatric and elderly patients and, additionally, will address the criteria used to determine whether patients were indeed atypical in their presentation.

B. Studies and experience with the LeuTech product:

Study Type and Phase of product development			# of Patients
Open label to evaluate HAMA -		Phase 1	30 patients
Open label to evaluate biodistribution -		Phase 1	10 patients
Open label within-patient comparative Patients with suspected appendicitis -		Phase 2	56 patients
Open label within-patient comparative Patients with suspected appendicitis -		Phase 3	203 patients
Other Studies:			
osteomyelitis	ongoing -	Phase 2	8 patients
Infectious process	ongoing -	Phase1/2	69 patients
Infectious process	completed (German) -	Phase 1	117 patients

Section II – Phase II

A. Investigational Plan Phase 2

Palatin initially conducted a phase II study in a small number of patients. The following the study and the data generated from it.

1. Study Objectives:

1) to assess the safety of Tc 99m LeuTechTm by monitoring vital signs and adverse events following its administration
2) To assess the efficacy by evaluating the diagnostic accuracy of Tc 99m LeuTechTm scintigraphy for the diagnosis of appendicitis and other inflammatory causes of right lower quadrant abdominal pain.
3) To assess the potential impact of the Tc 99m LeuTechTm study on the intended clinical management of the patient.

2. Study Size and Type:

The study was designed as an open-label multicenter study for evaluating the safety and efficacy of Tc 99m LeuTechTm for the detection of appendicitis. Fifty-six (56) patients at two study sites, 31 female and 25 male, were enrolled in and completed the study. 49 patients were at site A, and 7 were at site B. Patients were 8 years of age or older, with equivocal signs and symptoms of appendicitis, including right lower quadrant abdominal pain.

3. Inclusion Criteria

Female and male patients, 8 years of age or older, with right lower quadrant abdominal pain and equivocal presentation of appendicitis, were included. Equivocal presentation of appendicitis was to determined by the referring surgeon and had to include the presence of one or more of the following criteria:

- Atypical history/symptoms
- Atypical physical examination (e. g., absence of McBurney's point tenderness)
- Fever less than 101^0 f
- Atypical lab results (i.e., normal WBC count)

4. Exclusion Criteria

The following patients were excluded:

1. Females who were pregnant or nursing.

2. Females of childbearing potential, unless the possibility of current pregnancy could be ruled out by either B-HCG testing or by medical history.

3. Patients with a known sensitivity to murine (mouse) protein.

4. Patients who had previously been entered in this study or had received an investigational drug within 30 days of admission to this study.

5. Patients whose bodies contained radioactivity that may have interfered with the imaging procedure.

6. Patients with any physical condition rendering them unsuitable for radionuclide imaging (e.g., extreme obesity or physical deformity).

5. Patient Management:

The clinical utility of LeuTech was measured in this phase II study with a questionnaire given to surgeons. Prior to starting the Tc 99m LeuTechTm scan, the principal investigator was to ask the referring surgeon to complete a questionnaire specifying the intended clinical management course for the patient and rank his/her confidence in the management decision.

Categories of intended clinical management were:

"surgery",
"admission for clinical observation"
"send home"

Ranking of confidence in the management decision was as follows:

1 = low confidence
2 = moderate confidence
3 = high confidence

The principal investigator asked the surgeon to specify any additional diagnostic procedures that were anticipated.

Protocol Amendment #4 (March 3, 1998) modified the questionnaire to:

- provide for assessment of the likelihood of appendicitis, rather than confidence in the intended clinical management decision. This likelihood assessment would continue into the phase III study.

  - Almost definitely not appendicitis (0 - 19%)
  - Probably not appendicitis (20 - 39%)
  - Indeterminate appendicitis (40 59%)
  - Probably appendicitis (60 - 79%)
  - Almost definitely appendicitis (80 - 100%)

- Date and time fields were also added to the questionnaires to document the times the questionnaires were completed.

After reviewing the results of the Tc 99m LeuTechTm scan, but prior to treatment, the referring surgeon was asked to complete a second patient management questionnaire and provide a confidence score, using the same possibilities for management and the same rankings of confidence as described above.
The referring surgeon was to assume that the Tc 99m. LeuTechTm scan was highly sensitive and accurate for the diagnosis of appendicitis.

6. Efficacy Criteria:

1) Images were evaluated by the site investigators for the presence or absence of infection and, specifically, as "appendicitis" or "no appendicitis".

2) Images were evaluated by three experienced nuclear medicine practitioners. The blinded readers were to have no knowledge of patient identity, but were to be provided with pertinent medical history and a description of the patient's clinical signs and symptoms. Each image set was to be assigned a random code number that was to determine the order in which the images sets would be presented to the blinded readers; the randomization code number was the only identification.

a. The primary efficacy outcome measures:

- The patient-based agreement rate between the blinded readers' diagnosis and the final institutional diagnosis for appendicitis.

b. Secondary efficacy outcome measures:

- Patient-based rates of agreement of the individual site investigators' assessments of the Tc 99m LeuTechTm scans for the presence or absence of appendicitis with final institutional diagnosis.

- Associated measures of sensitivity, specificity, negative predictive value and positive predictive value for both blinded readers' and site investigators' assessments.

- Impact on clinical management as assessed by the comparison of the pre- and post-Tc 99m LeuTechTm imaging questionnaires.

3) Surgical and pathology reports were to be obtained for each patient who had surgery.

4) When no surgery was performed, results of the diagnostic tests were reviewed and the patient was contacted by telephone, at one month after the Tc 99m LeuTechTm procedure, to determine how the episode of right lower quadrant pain was resolved.

5) The referring surgeons were asked to indicate their intended clinical management prior to and after Tc 99m LeuTechTm study and to rate their confidence in their intended patient management decision.

7. Patient Monitoring:

1) Patients were directly observed during the first hour following administration of Tc 99m LeuTechTm. Vital signs (blood pressure, pulse and oral body temperature) were taken and recorded immediately prior to administration of Tc 99m LeuTechTm and at five minutes, 30 minutes and one hour post-administration.
2) Routine Laboratory evaluations prior to and after LeuTech administration

8. Statistical Methods:

- "SAS" software was used to generate all summary statistics and perform all analyses.
- The binomial distribution was used to obtain 95% confidence intervals for proportions.

B. Demographics:

Patient demographics are described below in tables 1-3. Parameters include age, weight, and height, in addition to gender and race.
Table 3 depicts the nature of patient's presenting sign with each symptom. These findings are consistent with those in the phase III trial, and will be discussed in more detail in section 3.

Table 1

SUMMARY STATISTICS FOR AGE, WEIGHT AND HEIGHT.					
	N	MIN.	MAX.	MEAN	STD.DEV.
AGE (yr.)	56	9.1	77.5	29.3	14.2
WEIGHT (kg)	56	29.5	104.5	65.9	17.9
HEIGHT (cm)	56	121.9	193.0	162.8	14.4

Table 2

DISTRIBUTION OF GENDER AND RACE.			
		N	%
GENDER	Female	31	55
	Male	25	45
	TOTAL	**56**	**100**
RACE	Caucasian	22	39
	Hispanic	28	50
	Black	3	5
	Oriental	2	4
	Filipino	1	2
	TOTAL	**56**	**100**

Table 3

DISTRIBUTION OF SIGNS AND SYMPTOMS THAT WERE CRITERIA FOR AN EQUIVOCAL PRESENTATION OF APPENDICITIS.		
	PATIENTS	
	N'	%
Atypical history and/or symptoms	34	61
Atypical physical examination (e.g., absence of McBurney's point tenderness)	18	32
Fever less than 101^0 F	44	79
Atypical lab results (i.e., normal WBC count)	21	38

Sum of the Ns exceeds the number of patients because some patients had more than one equivocal sign or symptom.

The use of other drugs in this trial is shown in table 4. Concomitant antibiotic use was somewhat more common in the phase III trial as compared to this trial. The role of antibiotic use and the scan results are discussed later in this document.

Table 4

DISTRIBUTION OF NON-STEROIIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) AND ANTIBIOTICS TAKEN WITHIN 24 HOURS OF Tc 99m LeuTechTm INJECTION.		
MEDICATION CLASS	NUMBER OF PATIENTS	(%)
NSAIDs	3	5
Antibiotics	5	9

Table 5

OTHER MEDICATIONS TAKEN WITHIN 24 HOURS OF Tc 99m LeuTechTm INJECTION.		
MEDICATION CLASS	NUMBER OF PATIENTS	(%)
Other Analgesics and Antipyretics	9	16
Intestinal Absorbents	3	5
None	33	59

1. Incidence of Appendicitis and other Infections:

The distribution of disease at the two sites is pertinent for site A, but the numbers for site B are so low that meaningful conclusions can not be made.

Table 6

DISTRIBUTION OF FINAL INSTITUTIONAL DIAGNOSIS FOR APPENDICITIS/NO APPENDICITIS AND INFECTION/NO INFECTION.				
	ACUTE APPENDICITIS		NO ACUTE APPENDICITIS	
	N	%	N	%
SITE A	26	53.1	23	47
SITE B	2	28.6	5	71
Total	28	50.0	28	50
	INFECTION		NO INFECTION	
	N	%	N	%
SITE A	29	59.2	20	41
SITE B	6	85.7	1	14
Total	35	62.5	21	38

Seven patients were diagnosed as having infections other than appendicitis, i.e. positive scans but not in the appendix zone. None of these patients went to surgery for suspected appendicitis. Pelvic inflammatory disease was not an exclusion criterion in this study, and two patients were diagnosed with PID, and did not go to surgery. PID was an exclusion criterion in the phase III trial.

Table 7

PATIENTS DIAGNOSED WITH INFECTION OTHER THAN "ACUTE APPENDICITIS".	
PATIENT	FINAL DIAGNOSIS
A-4	viral enteritis
A-11	mesenteric abscess versus hematoma
A-36	cytomegalovirus; colitis with acute ulceration
B-3	possibly intestinal infection and/or ovarian cyst
B-5	pelvic inflammatory disease
B-6	inflamed loop of bowel or GYN-related viscera but not abscess
B-7	PID/vaginitis, probable terminal ileitis

C. Primary Efficacy Results:

1. Blinded Readers Appendicitis

The phase II study used the agreement rate as the primary efficacy outcome measures. This is derived from the $((TP + TN)/N_{total}) \times 100$. Blinded reads were obtained. Of note, the sensitivity in this study for both the blinded readers and the onsite readers was higher than the specificity. This is comparable to the onsite readers in the phase III trial, but not the blinded readers. The phase III blinded readers had a higher specificity than sensitivity.

Table 8

BLINDED READER: Tc 99m LeuTechTm IMAGES, APPENDICITIS/NO APPENDICITIS.					
EVALUATION	N(t)	TP+ TN	Agreement Rate (%)	95% Confidence Int. LL	UL
READER1	56	41	73	60	83
READER2	56	46	82	69	90
READER3	56	41	73	60	83
AGGREGATE	56	**44**	**79**	65	88
EVALUATION	N(+)	TP	Sensitivity	95% Confidence Int. LL	UL
READER1	28	26	93	75	97
READER2	28	23	82	62	92
READER3	28	23	82	62	92
AGGREGATE	28	25	**89**	71	95
EVALUATION	N(-)	TN	Specificity	95% Confidence Int. LL	UL
READER1	28	15	54	34	71
READER2	28	23	82	62	92
READER3	28	18	64	44	80
AGGREGATE	28	19	**68**	47.6	82.2
EVALUATION	TP + FP	TP	PPV	95% Confidence Int. LL	UL
READER1	39	26	67	49.7	80
READER2	28	23	82	62.4	92
READER3	33	23	70	51.1	83
AGGREGATE	34	25	**74**	55.3	86
EVALUATION	TN + FN	TN	NPV	95% Confidence Int. LL	UL
READER1	17	15	88	62	95
READER2	28	23	82	62	92
READER3	23	18	78	56	90
AGGREGATE	22	19	**86**	64	94

Table 9

Reader-to-reader agreement was moderate but consistent for all pairs of readers, with concordance rates of 0.77 to 0.80 and kappa statistics of 0.34 to 0.45.

MEASURES OF INTER-READER AGREEMENT FOR DIAGNOSIS OF APPPENDICITIS/NO APPENDICITIS.		
Reader Comparisons	Concordance (95% Confidence Interval)	Kappa Statistic (95% Confidence Interval)
1 and 2	0.80 (0.67 to 0.89)	0.44 (0.17 to 0.71)
1 and 3	0.79 (0.65 to 0.87)	0.45 (0. 19 to 0.72)
2 and3	0.77 (0.63 to 0.86)	0.34 (0.06 to 0.62)

D. Secondary Efficacy results

1. Site Investigators: Appendicitis

Of note, the onsite readers did consistently better than the blinded readers. This difference is critical in evaluating the quality of the scan by independent evaluators with limited clinical information. As noted with the blinded readers, the sensitivity is higher than the specificity. The higher sensitivity for the onsite readers parallels the findings in the phase III trial, though the specificity is higher for the blinded readers than the onsite readers in the phase III trial.
Table 11 shows data for the onsite readers diagnosing appendicitis

Table 11

SITE INVESTIGATORS: PATIENT-BASED AGREEMENT RATE, SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF Tc 99m LeuTechTm IMAGES WITH FINAL INSTITUTIONAL DIAGNOSIS, APPENDICITIS/NO APPENDICITIS.

AGREEMENT RATE			Agreement	95% Confidence Int.	
	NT	TP+ TN	Rate (%)	LL	UL
SITE A	49	45	92	80	96.4
SITE B	7	4	57	20	82.4
Combined	56	49	**88**	75	93.8
SENSITIVITY				95% Confidence Int.	
	N(+)	TP	Sensitivity	LL	UL
SITE A	26	26	100	84	100
SITE B	2	1	50	3	84
Combined	28	27	**96**	80	97
SPECIFICITY				95% Confidence Int.	
	N(-)	TN	Specificity	LL	UL
SITE A	23	19	83	61	92
SITE B	5	3	60	17	85
Combined	28	22	**79**	59	90
POSITIVE PREDICTIVE			Positive	95% Confidence Int.	
VALUE	TP + FP	TP	Predictive Value	LL	UL
SITE A	30	26	87	68	94
SITE B	3	1	33	2	77
Combined	33	27	**82**	64	91
NEGATIVE PREDICTIVE			Negative	95% Confidence Int.	
VALUE	TN +FN	TN	Predictive Value	LL	UL
SITE A	19	19	100	79	100
SITE B	4	3	75.0	22	87
Combined	23	22	**96**	76	96

N_T is total number of patients with a final institutional diagnosis.
$N_{(+)}$ is total number of patients with a final institutional diagnosis of "acute appendicitis".
$N_{(-)}$ is total number of patients with a final institutional diagnosis of "no acute appendicitis".

E. Management:

Table 13 describes patients who had surgery, but ultimately were not diagnosed with appendicitis.

Table 13

PATIENTS UNDERGOING SURGERY WHOSE FINAL DIAGNOSIS WAS NEGATIVE FOR APPENDICITIS.					
PT.	FINAL DIAGNOSIS	INVESTIGATOR READ OF Tc 99m LeuTech SCAN	BLINDED READER1	BLINDED READER2	BLINDED READER3
A-14	No Infection	Acute Appendicitis	No Infection	No Infection	Acute Appendicitis
A-34	No Infection	Acute Appendicitis	Acute Appendicitis	No Infection	Acute Appendicitis
A-37	No Infection	Acute Appendicitis	Acute Appendicitis	Acute Appendicitis	No Infection

Of note, three patients went to surgery and were negative for appendicitis. The aggregate blinded read would be one true negative and two false positives.

Table 14 describes the clinical management and intended disposition of patients based on the surgeon questionnaire, both pre and post LeuTech scanning.

Table 14

DISTRIBUTION OF INTENDED CLINICAL MANAGEMENT PRE- AND POST-Tc: 99m LeuTechTm STUDY.				
Pre-Tc 99m LeuTechTm	Post-Tc 99m LeuTechTm			
	Send Home	Admit for Observation	Surgery	Pre-Total
Final Diagnosis = Acute Appendicitis				
Send Home	0	0	2	**2(7%)**
Admit for Observation	0	3	15	18(64%)
Surgery	0	0	8	8(3%)
Post-Total	**0(0%)**	3(11%)	25(89%)	28
Final Diagnosis = No Acute Appendicitis				
Send Home	4	0	0	4(14%)
Admit for Observation	13	6	1	20(71%)
Surgery	2	0	2	**4(14%)**
Post-Total	19(68%)	6(21%)	**3(11%)**	28

Two patients would have been sent home prior to LeuTech scanning, and none after LeuTech scanning. Four patients without appendicitis would have gone to surgery pre-scan, and three would have gone to surgery inappropriately post scan. In the group as a whole, the negative laparotomy rate was 5% (3 out of 56). The pre-scan rate would have been 7%.

1. Likelihood of Appendicitis

a) First half of study

Table 15 describes the likelihood estimates as recorded by the surgeons both pre and post scanning.

Table 15

DISTRIBUTION OF CONFIDENCE IN INTENDED CLINICAL MANAGEMIENT PRE- AND POST-Tc 99m LeuTechTm STUDY, N = 31*				
	Post-Tc 99m LeuTechTm Study			
Pre-Tc 99m LeuTechTm Study	Low	Moderate	High	Pre-Total
Final Diagnosis = Acute Appendicitis				
Low	0	1	1	2(13%)
Moderate	0	2	8	10(63%)
High	0	0	4	4(25.00%)
Post-Total	0	3(19%)	13(81%)	16
Final Diagnosis = No Acute Appendicitis				
Low	0	0	2	2(13%)
Moderate	1	3	8	12(80%)
High	0	0	1	1(7%)
Post-Total	1(7%)	3(20%)	11(73%)	15

*Number of patients studied when confidence item was in protocol.

In the first half of the study, the management questionnaire was less detailed as is reflected in table 15. For the second half of the study, the questionnaire that was used in the phase III trial was employed as is depicted in table 16. Both evaluations showed a shift in management decisions in a positive direction after the LeuTech scan compared with the pre-scan decision.

b) Second half of study

Table 16 reflects the change in the forms to estimate likelihood of appendicitis as determined by the surgeon. This format is used in the phase III trial.

Table 16

DISTRIBUTION OF ESTIMATES OF LIKELIHOOD OF APPENDICITIS PRE- AND POST-Tc 99m LeuTechTm STUDY, N = 25*

	Post-Tc 99m LeuTechTm Study					
Pre-Tc 99m LeuTechTm Study	Almost definitely not appendicitis' 0-19%	Probably not appendicitis 20-39%	Indeterminate appendicitis 40-59%	Probably appendicitis 60-79%	Definitely appendicitis 80-100%	Pre-Total
Final Diagnosis Acute Appendicitis						
Almost definitely not appendicitis	0	0	0	0	0	0
Probably not appendicitis	0	0	0	1	3	4(33%)
Indeterminate appendicitis	0	0	0	0	1	1(8%)
Probably appendicitis	0	0	0	2	4	6(50%)
Definitely appendicitis	0	0	0	0	1	1(8%)
Post-Total	0	0	0	3 (25%)	9 (75%)	12
Final Diagnosis No Acute Appendicitis						
Almost definitely not appendicitis	1	0	0	0	0	1(8%)
Probably not appendicitis	2	0	0	0	0	2(15%)
Indeterminate appendicitis	4	0	2	2	0	8(61%)
Probably appendicitis	1	0	0	1	0	2(15%)
Definitely appendicitis	0	0	0	0	0	0
Post-Total	8 (61%)	0	2(15%)	3 (23%)	0	13

*Number of patients studied when estimate of likelihood of appendicitis item was in protocol.
0 - 19% = Almost definitely not appendicitis;
20 - 39% = Probably not appendicitis;
40 - 59% = Indeterminate appendicitis;
60 - 79% = Probably appendicitis;
80 - 100% = Definitely appendicitis.

2. Likelihood Estimate Comparison:

Table 17 displays the comparison of pre-LeuTech estimates of likelihood of appendicitis in the phase II and phase III studies.

Table 17

Likelihood of Appendicitis	No Appy	Appy	Total	% Phase II	% Phase III
0-19%	1	0	1	4%	11%
20-39%	2	4	6	24%	31%
40-59%	8	1	9	36%	32%
60-79%	2	6	8	32%	22%
80-100%	0	1	1	4%	4%
Totals	13	12	25*		

*Only the last 25 patients out of the total 56 enrolled in the study had the likelihood estimates performed.

Although the numbers are similar, there is a trend for the phase II trial patients to have a higher likelihood of appendicitis. This is also represented in a 50% rate for appendicitis in the trial. The phase III trial shows a shift to a lower likelihood of appendicitis and a corresponding overall rate of ~30%. This could contribute to the higher sensitivity and lower specificity in the phase II trial versus the phase III trial.

F. Safety:

Table 18 shows the adverse events associated with the administration of LeuTech.

Table 18

ADVERSE EVENTS FOLLOWING ADMINISTRATION OF Tc 99m LeuTechTm						
Patient	Event (COSTART)	Severity	Min. Post Injection	Duration (Min.)	Related To Drug	Treatment
A-28	DYPSNEA	Mild	79	26	No	None
B-1	VASODILATATION	Mild	10	3	Possibly	None
B-3	VASODEIATATION	Mild	0	15	Probably	None

Three adverse events were reported; none were serious. All resolved with no specific therapy. Further safety data will be presented later.

G. Conclusions:

The following data summarizes the performance of LeuTech on the most important study parameters.

Agreement Rates-	Blinded Readers;	73-82%
	Aggregate;	79%
	On-Site;	88%
Sensitivity-	Blinded Readers;	82-93%
	Aggregate;	89%
	On-Site;	96%
Specificity-	Blinded Readers;	54-82%
	Aggregate;	68%
	On-Site;	79%
PPV-	Blinded Readers;	66-82%
	Aggregate;	73%
	On-Site;	82%
NPV-	Blinded Readers;	78-88%
	Aggregate;	86%
	On-Site;	96%

No significant adverse events were noted in the phase II study. Both on-site and off-site readers demonstrated favorably high levels of sensitivity, but lower specificity. These data may reflect the relatively high incidence of appendicitis in the population studied.

Section III – Phase III

A. Investigational Plan-Phase III

1. Study description

This study was designed to assess the efficacy and safety of Tc 99m LeuTechTm imaging for detection of acute appendicitis. The primary efficacy endpoints; were to be based on the image assessment of three blinded readers to avoid any possible bias from knowledge of other patient findings. The gold-standard comparator for efficacy was to be provided by each patient's final institutional diagnosis. For clinical laboratory measurements and vital signs, patients' pre-injection measurements were to provide baseline values for comparison with post-injection values to test for a possible drug effect.

The study was a prospective, multicenter, single-dose, within-patient, comparative clinical study of Tc 99m LeuTech Tm imaging in patients with equivocal signs and symptoms of appendicitis. A total of 200 patients [maximum of 40 patients (20%) per site] were to be enrolled at up to ten centers. Diagnostic accuracy was determined by measuring sensitivity and specificity of the imaging results against the final institutional diagnosis, which include surgery and pathology reports when surgery was performed, and two-week follow-up when surgery was not performed. In addition to image evaluations at the study site, blinded evaluations of the Tc 99m LeuTech Tm images were conducted by three readers who were not participating otherwise in the study. Clinical laboratory measurements and vital signs were to be collected pre- and post-Tc 99m LeuTechTm injection and adverse events were to be monitored for two hours following injection. Additionally, fifteen (15) of the 200 enrolled patients at selected sites were to be evaluated for production of HAMA.

2. Selection of Study Population

a. Inclusion Criteria

The major inclusion criteria are listed below:

Female and male patients, 5 years of age or older, with right lower quadrant (RLQ) abdominal pain, and equivocal presentation of appendicitis, were included. Equivocal presentation was determined by the referring surgeon and included the presence of one or more of the following criteria:

- Atypical history/symptoms, e.g.,
  - 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, e. g.,
  - absence of McBumey's point tenderness
  - absence of referred tenderness to RLQ with palpation in other quadrants
  - absence of abdominal muscular spasm with RLQ tenderness
- Fever less than 101^0F
- White blood cell (WBC less than $10{,}500/mm^3$)

b. Exclusion Criteria

The following patients were to be excluded:

1. Females who were pregnant or nursing.
2. Females of childbearing potential, unless the possibility of current pregnancy could be ruled out by urine or serum pregnancy testing.

3. Females with a diagnosis of pelvic inflammatory disease (PID).

4. Patients with a history of prior hospital admissions for abdominal pain of unknown etiology (original protocol) amended (Amendment #1, October 22, 1998) to state: patients with a history of two or more hospital admissions for abdominal pain of unknown etiology in the past six months.

5. Patients who had undergone US or CT imaging procedures (original protocol) amended (Amendment #1, October 22, 1998) to state: patients who have undergone CT imaging for work-up of the current episode of RLQ abdominal pain.

6. Patients with a known sensitivity to murine protein.

7. Patients who had previously been entered in this study or another Tc 99m LeuTech Tm study, or who had received an investigational drug within 30 days of admission to this study.

8. Patients whose bodies contained radioactivity that may have interfered with the imaging procedure.

9. Patients who, in the opinion of the investigator, had any physical condition rendering them unsuitable for radionuclide imaging (e.g., extreme obesity or physical deformity).

10. Patients for whom it was unlikely that two-week follow-up could be completed.

3. Removal of Patients from Therapy or Assessment

Patients were to meet all protocol eligibility criteria. Additionally, patients evaluable for efficacy were to have been imaged for at least 30 minutes and the Tc 99m LeuTech scans were to be deemed technically readable by the study investigator. For cases where surgery was not performed, patients for whom two week follow-up was not obtained were to be considered unevaluable.

Images from the first two patients at each site except the lead site (Site A) were to be considered training cases for the individual site investigators. The images were to be forwarded to the lead investigator (Samuel Kipper, M.D.), who was to review the images and image interpretations with the site investigators. These patients were to be considered not evaluable for analyses based on site investigators' evaluations only.

4. Treatment

a. Treatment Administered

Patients received a single intravenous injection of 0.3 ml - 0.5 ml Tc 99m LeuTech Tm containing 10 mCi - 20 mCi radioactivity and 75 Rg -125 gg antibody. The dose for patients less than 18 years of age was to be adjusted on a per kilogram body weight basis, using the following formula: 0.21 mCi per kilogram of body weight up to a maximum dose of 20 mCi. The injected dose was to satisfy all quality control tests prior to administration.

The original protocol stated that, following completion of the study, each image set was to be read in a blinded fashion by three experienced nuclear medicine practitioners, none of whom was participating as an investigator on this study. Protocol Amendment #1 modified the timing of blinded reader evaluation to take place "periodically through the course of the study." The blinded readers were provided only with the criteria for equivocal presentation of appendicitis as defined in the protocol and with patient demographic information (age, sex, height, weight), but were to have no knowledge of individual patient profiles or outcomes. Each image set was assigned a random code number that was to determine the order in which the image sets were presented to the readers. Each reader

independently evaluated all image sets, which were presented in a standard format on computer monitors, with only the randomization code number as identification. Image sets for each patient were evaluated as positive or negative for infection and the interpretation recorded on the CRF. Positive images were further classified as acute appendicitis or other infection.

Images from the first two patients at each site except the lead site (Site A) were to be considered training cases for the individual site investigators. The images were forwarded to the lead investigator (Samuel Kipper, M.D.), who reviewed the images and image interpretations with the site investigators. Image evaluation data of the first two patients at each site were not included in efficacy analyses based on investigators' evaluations of images.

b. Patient Management

Prior to receiving the results of the Tc 99m LeuTechTm scan, the principal investigator asked the referring surgeon to complete a questionnaire estimating the likelihood that the patient had appendicitis according to the following categorization:

almost definitely not appendicitis	(0 - 19%)
probably not appendicitis	(20 - 39%)
indeterminate appendicitis	(40 - 59%)
probably appendicitis	(60 - 79%)
almost definitely appendicitis	(80 - 100%)

The principal investigator also asked the surgeon to specify the intended clinical management course for the patient as follows:

surgery
admit for clinical observation
send home

The surgeon was to specify any, additional diagnostic procedures that were anticipated.

After reviewing the results of the Tc 99m LeuTech Tm scan, but prior to treatment and without information from any additional diagnostic tests, the referring surgeon was to complete a post-scan questionnaire, estimating the

likelihood of appendicitis and the intended clinical management course for the patient. For purposes of completing this questionnaire, the referring surgeon was to assume that the Tc 99m LeuTechTm scan was highly sensitive and accurate for the diagnosis of appendicitis. The principal investigator was to assure that the referring surgeon completed both questionnaires for each patient according to the schedule outlined.

The final institutional diagnosis was to be recorded on the CRF. If a patient underwent surgery, copies of the surgical report and pathology report were to be attached to the CRF. In surgical cases that were negative for appendicitis, the pathology lab was to store the tissue for a minimum of two years for possible further analysis. In the event surgery was not performed, two-week follow-up was to be obtained. Patients were to be given stamped, addressed postcards to complete and return with two-week follow-up information. If a follow-up postcard was not received, the patient was to be contacted by telephone to obtain the clinical follow-up. If appropriate, reports of any subsequent hospital and/or physician visits, tests or treatment were to be obtained and reviewed. In addition, results from additional diagnostic procedures (e.g., ultrasound, spiral or conventional CT) were to be obtained and recorded on the CRF.

c. Clinical Laboratory Evaluations

The original protocol stated that clinical laboratory studies were to be performed in all patients within two hours prior to Tc 99m LeuTechTm injection. Protocol Amendment #1 (October 22, 1998) changed the timing of the clinical laboratory studies from within two hours to within eight hours prior to injection. They were to be repeated at two hours following administration of Tc 99m LeuTechTm or immediately prior to surgery or discharge, whichever came first. The following studies were to be performed:

1) Hematology:

hematocrit	white blood cell (WBC) count
hemoglobin	WBC differential
platelet count	red blood cell (RBC) count

2) Clinical chemistry

aspartate transaminase (AST) (SGOT)	total bilirubin
alanine transaminase (ALT) (SGPT)	total protein
alkaline phosphatase	blood urea
nitrogen (BUN)	
lactate dehydrogenase (LDH)	serum creatinine

Protocol Amendment #1 also specified that blood samples (5 ml each) for baseline HAMA studies were to be collected from 15 patients at selected sites within eight hours prior to the Tc 99m LeuTechTm injection and again at 3 to 4 weeks following the Tc 99m LeuTechTm injection. Sites A, D, E and H enrolled patients for HAMA measurements. Samples were to be collected in red-top tubes (no anticoagulant) and allowed to clot. Following centrifugation, serum was to be separated and aliquots of approximately 1 ml serum were to be stored frozen ($\leq -20^0$ C) in polypropylene cryogenic tubes. One of the pair of duplicate specimens was to be kept at the site and the other was to be shipped on dry ice to the laboratory where the HAMA analyses were performed.

Each sample was to be assayed for HAMA in duplicate, with results reported in nanograms of RB5 IgM, which would bind to the HAMA in one milliliter of serum.

A patient was considered as having a positive HAMA response at a post-dose follow-up time if the post-injection HAMA level was greater than or equal to four times the pre-injection value for that patient. Patients who were positive for a HAMA response at 3 to 4 weeks were to have blood samples taken again at 12 to 16 weeks and evaluated in the same manner.

5. Non-Evaluable Patients

Table 1 represents patients that were non-evaluable for the phase III study. This represent only ~1% of the study patients.

Table 1

PATIENTS NOT EVALUABLE FOR EFFICACY AND REASONS FOR THEIR EXCLUSION.	
PATIENT	REASON
A-14	Lost to follow-up
D-07	Lost to follow-up
E-09	Imaged for less than 30 minutes post-injection

- Patient A-14 was considered positive for acute appendicitis but left the hospital of his own accord without going to surgery. He reportedly returned to Mexico for surgery and attempts to locate him for follow-up were unsuccessful.

- Patient D-7 was negative and moved without leaving a forwarding address prior to the two-week follow-up.

- Patient E-09 had a positive scan and was taken to surgery after 24 minutes of scanning. This is less than the 30 minutes required by protocol. The blinded reads of this scan were negative for appendicitis. The pathology report confirmed a positive appendicitis for this patient.

B. Demographics

The demographics of patients enrolled in the phase III trial including their presenting signs and symptoms, distribution by gender and race, summary statistics for age, weight, height and BMI are presented below in tables 2-4.

Table 2:

Distribution of Signs and Symptoms Comprising Equivocal Presentation of Appendicitis		
	PATIENTS	
	N[1]	%
Atypical history and/or symptoms	148	73
Atypical physical examination	138	68
Fever less than 101 ^{0}F	185	91
WBC count < 10,500/mm'	115	57
1 Sum of N is greater than number of patients because some patients had more than one equivocal sign or symptom		

Table 3:

DISTRIBUTION OF GENDER AND RACE			
		N	%
GENDER	Female	121	60
	Male	82	40
	TOTAL	203	100
RACE	White ,	149	73
	Hispanic	32	16
	Black	16	8
	Other	6	3
	TOTAL	203	100

Table 4:

SUMMARY STATISTICS FOR AGE, WEIGHT, HEIGHT AND BMI [1]					
	N	MIN.	MAX.	MEAN	STD. DEV.
AGE (yr)	203	5.2	85.9	30.5	16.5
WEIGHT (kg)	203	21.4	127.3	69.2	20.8
HEIGHT (cm)	201	104.1	198.1	165.2	14.4
BMI 1	201	12.6	46.7	25	5.8
1 BMI = weight (kg)/ height ^{2} (m)					
The National Center for Health Statistics defines overweight as: BMI (men) $\geq$ 27.8 and BMI (women) $\geq$ 27.3					

a. Patient Distribution by Site

The distribution of patients enrolled at a given site and the incidence of appendicitis at the various sites is displayed in table 5. This is followed by the incidence of appendicitis at the various sites in table 6.

Table 5:

DISTRIBUTION OF PATIENTS ENROLLED BY SITE		
SITE	**N**	**% of patients in the Study**
A	39	19
B	19	9
C	7	4
D	23	11
E	29	14
F	3	2
G	11	5
H	3	18
I	8	4
J	28	14
Total	203	100

Table 6:

DISTRIBUTION OF FINAL INSTITUTIONAL DIAGNOSIS FOR APPENDICITIS/NO APPENDICITIS AND INFECTION/ NO INFECTION, EVALUABLE PATIENTS.				
	Appendicitis N(%)	No Appendicitis N(%)	Infection N(%)	No Infection N(%)
SITE A	10(26)	28(74)	19(50)	19(50)
SITE B	3(16)	16(84)	6(32)	13(68)
SITE C	0	7(100)	2(29)	5(71)
SITE D	8(36)	14(64)	9(41)	13(59)
SITE E	3(11)	25(89)	6(21)	22(79)
SITE F	1(33)	2(67)	1(33)	2(67)
SITE G	4(36)	7(64)	5(46)	6(55)
SITE H	15(42)	21(58)	17(47)	19(53)
SITE 1	6(75)	2(25)	7(88)	1(13)
SITE J	9(32)	19(68)	10(36)	18(64)
TOTAL	**59(30)**	**141(71)**	**82(41)**	**118(59)**

There is a wide variation in the distribution of patients at the 10 sites ranging from over 19% of patients, down to 2% of patients. There was also a wide variation in the incidence of appendicitis ranging from 0% to 75%. This reflects the somewhat loose entrance criteria regarding equivocal appendicitis.

b. Distribution of Surgical patients

Table 7 represents the patients by site, which went to surgery.

Table 7

Distribution of Patients who Underwent Surgery.

SITE	#SURGERY PATIENTS	# ACUTE APPENDICITIS	OTHER FINDINGS	# NEGATIVE PATIENTS
A	13	10	1 ruptured bladder (A- 15)	1
			1 periappendicitis (A-21)	
B	5	3	1 retrocecal abscess (B-12)	1
C	2	0	1 periappendicitis (C-02)	0
			1 Crohn's disease with impending	
			obstruction (C-03)	
D	9[1]	9	0	1
E	4	3	1 perforated gall bladder (E- 12)	0
F	1	1	0	0
G	4	4	0	0
H	17	15	1 rupt. diverticulitis/ abscess (H-34)	1
I	7	6	0	1
J	12[1]	9	0	3
ALL	74	59	7	8

[1]D-08, J- 19 and J-28 were negative according to all readers of Tc 99m LeuTechTm images and final institutional diagnoses were negative.

Within this study, 74 patients when to surgery. Of these patients, 59 were found to have the diagnosis of acute appendicitis. 7 patients were found to have other surgical etiologies for their suspected appendicitis, and 8 patients had negative laparotomies. The rate of negative laparotomy was 11% in a patient population that was selected to have atypical signs and/or symptoms.

C. Efficacy

1.Appendicitis/No Appendicitis

The investigator at each study site evaluated the Tc 99m LeuTech images for each patient and recorded the results. The first two patients at each site other than the lead site constituted the training cases. The site investigator's evaluation however as recorded on the case report forms (CRFs) were not changed as a result of reviewing them with the lead investigator, and efficacy indicators were calculated excluding (n=182) and including the training cases (N=200) at each site.

Blinded reader evaluations are based on the individual reads of the three blinded readers and their aggregate. The majority read (at least 2 out of 3 readers agreeing for an individual patient) determined the aggregate. The blinded reads were based on the 200 evaluable patients though an intent to treat (ITT) analysis is also provided. The three non-evaluable patients were considered worse case scenarios (1-FP and 2-FN)

Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio LR(+) and negative likelihood ratio LR(-) of the Tc 99m LeuTechTm diagnosis are defined as:

Sensitivity = (TP/TP + FN) x 100

Specificity = (TN/TN + FP) x 100

Accuracy = (TP + TN / TP +FN+TP + TN) x 100

Positive Predictive Value = TP / (TP + FP) x 100

Negative Predictive Value = TN / (TN + FN) x 100

Likelihood Ratio, Positive (LR+) =TP/FP / (TP + FN)/(FP+TN)

Likelihood Ratio, Negative (LR-)= FN/TN / (TP + FN)/(FP+TN)

TP is the number of true positive outcomes,
TN is the number of true negative outcomes,
FP is the number of false positive outcomes,
FN is the number of false negative outcomes.

As noted earlier, on-site investigators had their first two cases designated as training cases. The efficacy analysis was prospectively defined to exclude the training cases, though as noted from the data, the inclusion of the training cases did not impact the final analysis. Also of note, for the site investigators, the sensitivity was higher than the specificity. As will be seen, this is not the case for the blinded readers.

a. Site Investigators

Table 8 shows the on-site investigators efficacy outcome measures. These include sensitivity, specificity, accuracy, PPV and NPV.

Table 8

EVALUATION	N(+)	TP	**SENSITIVITY**	95% LL
Excluding Training Cases	54	49	91	81
Including Training Cases	**59**	**53**	**90**	**81**
	N(-)	TN	**SPECIFICITY**	95% LL
Excluding Training Cases	128	110	86	80
Including Training Cases	**141**	**122**	**87**	**81**
	N(t)	TP + TN	**ACCURACY**	95% LL
Excluding Training Cases	182	159	87	82
Including Training Cases	**200**	**175**	**88**	**83**
	TP + FN	TP	**PPV**	95% LL
Excluding Training Cases	67	49	73	63
Including Training Cases	**72**	**53**	**74**	**64**
	TN + FN	TN	**NPV**	95% LL
Excluding Training Cases	115	110	96	91
Including Training Cases	**128**	**122**	**95**	**91**

N (t) is total number of patients with a final institutional diagnosis.
N (+) is total number of patients with a final institutional diagnosis of "acute appendicitis".

Sensitivity with and without training cases was approximately 90% and Specificity was 86%. Accuracy, PPV and NPV were approximately 87%, 73% and 95% respectively. The secondary efficacy outcome measure for on-site readers specified the exclusion of the training cases, but the data shows very little difference between the two patient populations.

b. Blinded Readers- Evaluable Patients

Table 9 depicts the efficacy outcome measures for the blinded readers. This is based on 200 evaluable patients. An intent to treat analysis using the worse case scenario for the 3 missing patients will be shown later. No significant differences between evaluable and intent to treat patient populations are observed.

Table 9

SENSITIVITY				
EVALUATION	N (+)	TP	Sensitivity	95% Lower Limit
Blinded Reader 1	59	48	81	71
Blinded Reader 2	59	39	66	55
Blinded Reader 3	59	45	76	65
Aggregate	59	44	75	63
SPECIFICITY				
EVALUATION	N(-)	TN	Specificity	95% Lower Limit
Blinded Reader 1	141	124	88	82
Blinded Reader 2	141	127	90	85
Blinded Reader 3	141	133	94	90
Aggregate	141	131	93	88
ACCURACY				
EVALUATION	N (T)	TP+TN	**Accuracy**	95% Lower Limit
Blinded Reader 1	200	172	86	81
Blinded Reader 2	200	166	83	78
Blinded Reader 3	200	178	89	85
Aggregate	200	175	88	83
POSITIVE PREDICTIVE VALUE				
EVALUATION	TP + FP	TP	**PPV**	95% Lower Limit
Blinded Reader 1	65	48	74	63
Blinded Reader 2	53	39	74	62
Blinded Reader 3	53	45	85	74
Aggregate	54	44	82	70
NEGATIVE PREDICTIVE VALUE				
EVALUATION	TN + FN	TN	**NPV**	95% Lower Limit
Blinded Reader 1	135	124	92	87
Blinded Reader 2	147	127	86	81
Blinded Reader 3	147	133	91	85
Aggregate	146	131	90	85

N (+) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N (-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis
N (T) is the total number of evaluable patients

The blinded readers had much better specificity vs. sensitivity and a better NPV. The blinded readers also had a better specificity than any of the other studies as well.

c. Intent to Treat

Table 10 shows the intent to treat analysis.

Table 10

EVALUATION	N(+)	TP	**Sensitivity**	95% Lower Limit
Blinded Reader 1	61	48	79	68
Blinded Reader 2	61	39	64	53
Blinded Reader 3	61	45	74	63
Aggregate	61	44	72	61
EVALUATION	N(-)	TN	**Specificity**	95% Lower Limit
Blinded Reader 1	142	124	87	82
Blinded Reader 2	142	127	89	84
Blinded Reader 3	142	133	94	89
Aggregate	142	131	92	87
EVALUATION	N (T)	TP+TN	**Accuracy**	
Blinded Reader 1	203	172	85	
Blinded Reader 2	203	166	82	
Blinded Reader 3	203	178	88	
Aggregate	203	175	86	
EVALUATION	TP + FP	TP	**PPV**	
Blinded Reader 1	67	48	72	
Blinded Reader 2	55	39	71	
Blinded Reader 3	55	45	82	
Aggregate	56	44	79	
EVALUATION	TN + FN	TN	**NPV**	
Blinded Reader 1	137	124	91	
Blinded Reader 2	149	127	87	
Blinded Reader 3	149	133	90	
Aggregate	148	131	89	

N (+) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N (-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis.
N (T) is the number of patients whose images were evaluated by the reader.

This phase III study enrolled 203 patients. Of those 203, 200 were evaluable. Analyzing the intent to treat (ITT) population did not alter the results of the study, even when the worse case scenario was taken for those patients i.e. they were a false positive or false negative case.

d. Comparison of Evaluable Patients and Intent to Treat

A direct comparison is made between the intent to treat patients using the worse case scenario and the evaluable patients for the individual blinded readers. This is directly compared to the onsite readers both with and without the training cases included. There are noted minor decreases in all parameters.

Table 11

	Sensitivity	Specificity	Accuracy	PPV	NPV
Blinded Reader 1 ITT (203)	79	87	85	72	91
Blinded Reader 1 Eval (200)	81	88	86	74	92
Blinded Reader 2 ITT (203)	64	89	82	71	87
Blinded Reader 2 Eval (200)	66	90	83	74	86
Blinded Reader 3 ITT (203)	74	94	88	82	90
Blinded Reader 3 Eval (200)	76	94	89	85	91
Blinded Reader Agr ITT (203)	72	92	86	79	89
Blinded Reader Agr Eval (200)	75	93	88	82	90
On-Site Readers w/o Training (182)	91	86	87	73	96
On-Site Readers with Training (200)	90	86	88	74	95

This phase III study enrolled 203 patients. Of those 203, 200 were evaluable. Analyzing the intent to treat (ITT) population did not alter the results of the study, even when the worse case scenario was taken for those patients i.e. they were a false positive or false negative case.

e. Agreement among Tc 99m LeuTechTm Blinded Readers

As provided by the sponsor, the results of the Tc 99m LeuTechTm blinded readers were evaluated for agreement using the kappa statistic and concordance rate (the rate of agreement between readers). Measures of inter-reader agreement evaluated agreement for each pair of blinded readers for the diagnosis of appendicitis/no appendicitis, using evaluable patient data. Agreement between a pair of readers for an individual patient was based on whether patient diagnosis agreed with (TP or TN), or did not agree with (FP or FN), final institutional diagnosis.

1. Concordance

Table 12 shows the blind reader concordance rate.

Table 12

PAIRS OF BLINDED READERS	CONCORDANCE RATE, (95% CONFIDENCE INTERVAL)	KAPPA STATISTIC (95% CONFIDENCE INTERVAL)
1,2	0.88 (0.82 - 0.92)	0.54 (0.38 - 0.70)
1,3	0.90 (0.84 - 0.93)	0.54 (0.37 - 0.72)
2,3	0.89 (0.84 - 0.93)	0.55 (0.38 - 0.71)

Reader-to-reader agreement was good for all pairs of readers, with concordance rates of 0.88 to 0.90 and kappa statistics of 0.54 and 0.55.

2. Likelihood Ratios:

Table 13 depicts the likelihood ratios that a positive scan increases the probability of having appendicitis, and a negative scan decreases the probability.

Table 13

EVALUATION	LR(+)	95% Confidence Interval	LR(-)	95% Confidence Interval
Blinded Reader 1	6.75	4.25-10.71	0.21	0.12-0.36
Blinded Reader 2	6.66	3.92-11.31	0.38	0.26-0.54
Blinded Reader 3	13.44	6.76-26.75	0.25	0.16-0.40
Aggregate	10.52	5.68-19.46	0.27	0.18-0.43

Patients whose images were evaluated as positive for appendicitis had a likelihood of having appendicitis 6 to 13 times greater post-test than their likelihood of having appendicitis pre-test. Given the aggregate blind read results, the odds that a patient has appendicitis increase by a multiple of 10, if the Tc 99m LeuTechTm study is positive. For images evaluated as negative for appendicitis, the odds that a patient has appendicitis decrease by a factor 115 to 1/3 of their pre-test likelihood. Given the aggregate blind read results, a negative Tc 99m LeuTechTm study decreased the odds that a patient had appendicitis by a factor of approximately 1/4.

D. Subgroup analysis

The primary efficacy parameters were evaluated in several subgroups of patients including pediatric patients and the elderly. Individual blinded reader data in addition to the aggregate and on-site readers is included. The total number of patients in this study under the age of 18 is 48. Those over the age of 65 are 10. Pooled data from the phase II study will be presented later.

The efficacy parameters for the individual groups essentially mirror the efficacy of the entire study population. The sensitivity in the elderly population is better, though it is only based on 4 positive cases.

Despite lower numbers at the two ends of the age spectrum, the overall trends reveal a consistency in the data that applies to the age groups defined by the sponsor.

1. Age group

The following table shows the efficacy outcome measures for the various age groups. Further data will be presented later.

Sensitivity and Specificity-Subgroups: 5-17,18-64, >65 Years, Evaluable Patients.

Table 14

SENSITIVITY

	5 - 17 yr			18 - 64 yr			65 yr				
	N(+)	TP	Sens.	N(+)	TP	Sens.	N(+)	TP	Sens.	Chi Squ	Sig. Prob.
Bl. Rdr I	11	11	100	44	33	75	4	4	100	4.609	0.1
Bl. Rdr 2	11	8	73	44	28	64	4	3	75	0.476	0.788
Bl. Rdr 3	11	7	64	44	34	77	4	4	100	2.239	0.326
Agg.	11	8	73	44	32	73	4	4	100	1.463	0.481
Inves	10	9	90	40	37	93	4	3	75	1.333	0.513

SPECIFICITY

	5 - 17 yr			18 - 64 yr			65 yr				
	N(-)	TN	Spec.	N(-)	TN	Spec.	N(-)	TN	Spec.	Chi Squ	Sig. Prob.
Bl. Rdr 1	37	33	89	98	87	89	6	4	67	2.68	0.262
Bl. Rdr 2	37	34	92	98	87	89	6	6	100	0.983	0.612
Bl. Rdr 3	37	36	97	98	94	96	6	3	50	23.102	< 0.001
Agg.	37	35	95	98	91	93	6	5	83	0.995	0.608
Inves.	35	31	89	87	74	85	6	5	83	0.29	0.865

ACCURACY

	5 -17 yr			18 - 64 yr			≥65 yr		
	N(T)	TP+TN	**Acc.**	N(T)	TP+TN	**Acc.**	N(T)	TP+TN	**Acc.**
Bl. Reader 1	48	44	92	142	120	85	10	8	80
Bl. Reader 2	48	42	88	142	115	81	10	9	90
Bl. Reader 3	48	43	90	142	128	90	10	7	70
Aggregate	48	43	90	142	123	87	10	9	90
Investigator	45	40	89	127	111	87	10	8	80

POSITIVE PREDICTIVE VALUE

	5 - 17 yr			18 - 64 yr			≥65 yr		
	TP+FP	TP	**PPV**	TP+FP	TP	**PPV**	TP+FP	TP	**PPV**
Bl. Reader 1	15	11	73	44	33	75	6	4	67
Bl. Reader 2	11	8	73	39	28	72	3	3	100
Bl. Reader 3	8	7	88	38	34	90	7	4	57
Aggregate	10	8	80	39	32	82	5	4	80
Investigator	13	9	69	50	37	74	4	3	75

NEGATIVE PREDICTIVE VALUE

	5 - 17 yr			18 - 64 yr			≥65 yr		
	TN+TN	TN	**NPV**	TN+TN	TN	**NPV**	TN+TN	TN	**NPV**
Bl. Reader 1	33	33	100	98	87	89	4	4	100
Bl. Reader 2	37	34	92	103	87	85	7	6	86
Bl. Reader 3	40	36	90	104	94	90	3	3	100
Aggregate	38	35	92	103	91	88	5	5	100
Investigator	32	31	97	77	74	96	6	5	83

N(+) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N(-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis.

2. Comparison of Gender Subgroups, Evaluable Patients.

Table 15 compares gender using all evaluable patients.

Table 15

SENSITIVITY								
	FEMALE			MALE				
	N(+)	TP	Sensitivity	N(+)	TP	Sensitivity	Chi Squ	Sig. Prob.
Blinded Reader 1	30	28	93	29	20	69	5.773	0.016
Blinded Reader 2	30	23	77	29	16	55	3.043	0.081
Blinded Reader 3	30	25	83	29	20	69	1.682	0.195
Aggregate	30	25	83	29	19	66	2.469	0.116
Investigators	27	25	93	27	24	90	0.22	0.639
SPECIFICITY								
	FEMALE			MALE				
	N(-)	TN	Specificity	N(-)	TN	Specificity	Chi Squ	Sig. Prob.
Blinded Reader 1	91	83	91	50	41	82	2.581	0.108
Blinded Reader 2	91	85	93	50	42	84	3.193	0.074
Blinded Reader 3	91	89	98	50	44	88	5.793	0.016
Aggregate	91	87	96	50	44	88	2.832	0.092
Investigators	82	71	87	46	39	85	0.079	0.778

The sponsor also separated male and female patients and found no differences in the efficacy parameters. This will be further broken done by age group to look specifically at the primary reproductive years for women which has historically presented a greater diagnostic challenge. Those data will be presented in a later section.

3. Comparison of Race Subgroups, Evaluable Patients.

Table 16 separates races into whites and all others.

Table16

SENSITIVITY								
	WHITE			ALL OTHER				
	N(+)	TP	Sensitivity	N(+)	TP	Sensitivity	Chi Squ	Sig.Prob.
Blinded Reader 1	44	36	82	15	12	80	0.024	0.876
Blinded Reader 2	44	27	61	15	12	80	1.734	0.188
Blinded Reader 3	44	33	75	15	12	80	0.155	0.694
Aggregate	44	32	73	15	12	80	0.312	0.576
Investigators	41	36	88	13	13	100	1.747	0.186
SPECIFICITY								
	WHITE			ALL OTHER				
	N(-)	TN	Specificity	N(-)	TN	Specificity	Chi Squ	Sig.Prob.
Blinded Reader 1	103	94	91	38	30	79	3.97	0.046
Blinded Reader 2	103	93	90	38	34	90	0.0207	0.886
Blinded Reader 3	103	97	94	38	36	95	0.016	0.898
Aggregate	103	96	93	38	35	92	0.051	0.822
Investigators	93	80	86	35	30	86	0.002	0.965

N(+) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N(-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis.

The sponsor also explored the possibility of race affecting outcome and found no significant differences within the study.

4.Comparison of BMI Subgroups, Evaluable Patients.[1]

Table 17 shows patient subgroups based on weight.

Table 17 (sponsor)

SENSITIVITY								
	BMI < 27			BMI ≥ 27				
	N(+)	TP	Sensitivity	N(+)	TP	Sensitivity	Chi Squ	Sig. Prob.
Blinded Reader 1	42	35	83	15	11	73	0.71	0.4
Blinded Reader 2	42	27	64	15	10	67	0.027	0.868
Blinded Reader 3	42	32	76	15	11	73	0.049	0.825
Aggregate	42	32	76	15	10	67	0.517	0.472
Investigators	39	37	95	13	10	77	3.614	0.057

SPECIFICITY								
	BMI < 27			BMI ≥27				
	N(-)	TN	Specificity	N(-)	TN	Specificity	Chi Squ	Sig. Prob.
Blinded Reader 1	96	83	87	45	41	91	0.626	0.429
Blinded Reader 2	96	87	91	45	40	89	0.103	0.748
Blinded Reader 3	96	90	94	45	43	96	0.187	0.666
Aggregate	96	88	92	45	43	96	0.703	0.402
Investigators	85	75	88	43	35	82	1.105	0.293

N(+) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N(-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis.

[1] Height and weight was not recorded for 2 patients, total N = 198.

Additionally, weight based on the BMI was explored as a factor that could influence the sensitivity or specificity of the study. Though there was no statistically significant differences noted, the sensitivity for the onsite readers did drop and almost reached statistical significance. However, the total number of positive cases was small. This was not observed with the blinded readers to the same degree. The specificity actually improved in all groups in the heavier subjects.

5. Enrollment Order

Table 18 shows the comparison of patients by the order in which they presented.

Table 18

APPENDICITIS							
FIRST 5 PATIENTS			OTHER PATIENTS				
N(+)	TP	**Sensitivity**	N(+)	TP	**Sensitivity**	Chi Squ	Sig. Prob.
11	9	82	48	44	92	0.95	0.33
N(-)	TN	**Specificity**	N(-)	TN	**Specificity**		
37	30	81	104	92	89	1.275	0.259

N(+) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N(-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis.

Though there was a trend towards improvement in comparing the first 5 patients enrolled to the subsequent patients, it did no reach statistical significance. As was shown earlier, there was not a major difference for the onsite readers with or without the training cases. This would imply that there is not a difficult learning curve for this product.

E. FDA Review and Analysis - Phase Three Trial

1. Efficacy Outcome Measures with Regard to Likelihood of Appendicitis

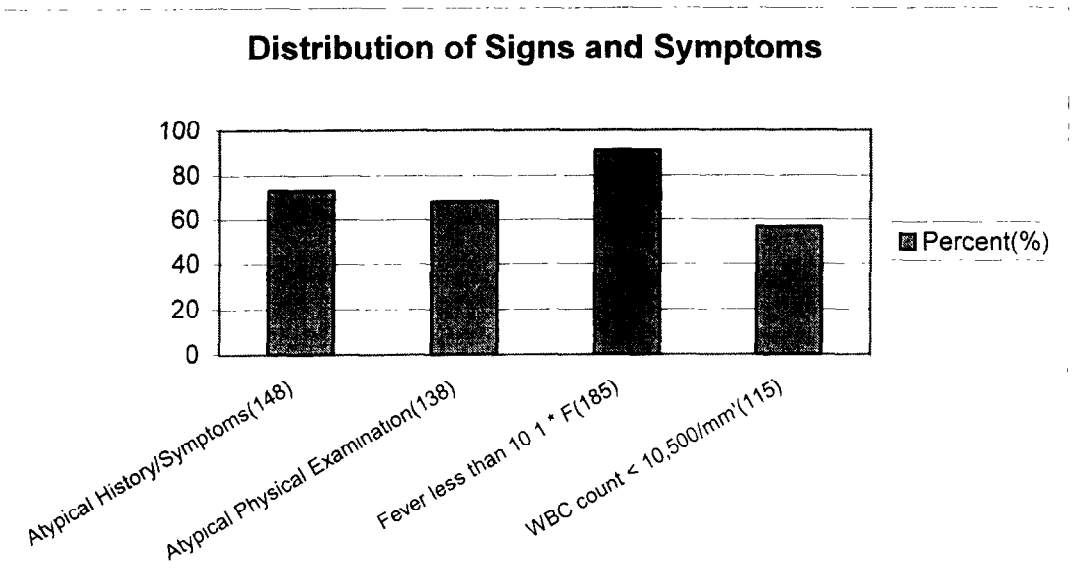
The distribution of the 4 major entrance criteria for this study is reviewed below. Almost all patients had a fever under 101^0F and the majority met at least one of the other major criteria. Table 19 depicts the distribution of the major signs and symptoms as derived from the entrance criteria.

Table 19

	PATIENTS	
	N[1]	%
Atypical history and/or symptoms	148	73
Atypical physical examination	138	68
Fever less than 101^0 F	185	91
WBC count < 10,500/mm'	115	57

1- **Sum of N is greater than number of patients because some patients had more than one equivocal sign or symptom**

Chart 1



2. Atypical Signs and symptoms

The entrance criteria for this study allowed patients with a very low probability of having appendicitis, and patients with a very high probability of having appendicitis to be entered into the study. This is reflected by the fact that patients only needed one finding from the list of atypical findings for appendicitis, or could have all eleven criteria and qualify for the study. Depending on how investigators used these criteria, it created a range in the incidence of appendicitis at given sites from a low of 0% to a high of 75%. Even breaking down the individual entrance criteria into their component parts a consistent correlation between that criterion and the incidence of appendicitis could not be established. The criterion that came closest was a normal vs. abnormal WBC.

As part of the management portion of the study, surgeons were asked to rank their impression of the likelihood of appendicitis prior to obtaining the LeuTech scan. The surgeons ranked the probability of appendicitis from 0 to 19 percent, 20 to 39 percent, 40 to 59 percent, 60 to 79 percent, and 80 to 100 percent. This pre-scan ranking correlated nicely with the true rate of appendicitis in the given groups. When the surgeons felt there was a 0 to 19% chance of appendicitis, they were correct. 22 patients fell into this category; none had appendicitis for a 0% rate. On the other hand when the surgeons felt that there was an 80 to 100% chance of appendicitis 87.5% of patients actually had appendicitis. Though this was designed into the study as a management tool, in fact it created a way to narrow down the patient pool to those that more clearly represent atypical appendicitis, and address the utility of this product in those patients.

The following tables and charts display these data:

Table 20

Surgeons pre scan likelihood of appendicitis N(T)	N(a)	Rate
0-19% (22)	0	0.0%
20-39% (61)	9	15%
40-59% (65)	16	25%
60-79% (44)	27	61%
80-100% (8)	7	88%
20-70% (170)	52	31%

N (a) – number of patients with a final diagnosis of appendicitis

Chart 2

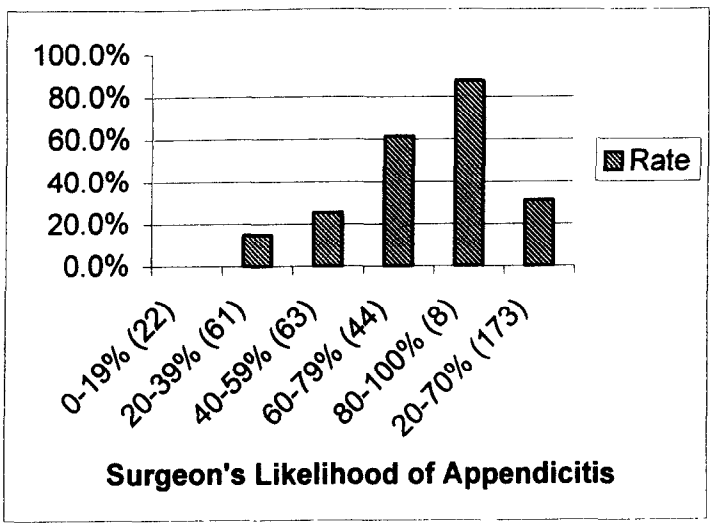
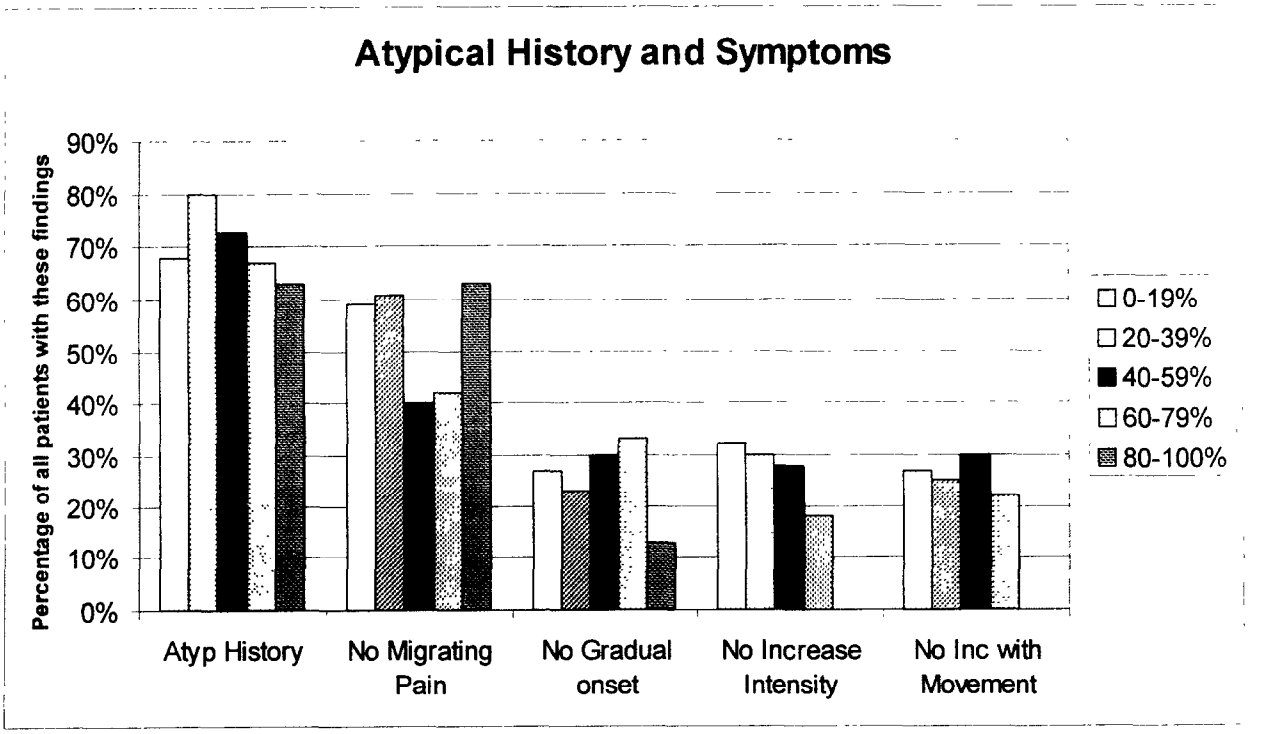


Table 21

% Chance	Atyp History	No Migrating Pain	No Gradual onset	No Increase Intensity	No Inc. pain with Movement	Atyp PE	No McB point tenderness	No Referred pain with palpation	No Spasm	Fever <101	Norm WBC
0-19%	68%	59%	27%	32%	27%	73%	14%	45%	55%	91%	82%
20-39%	80%	61%	23%	30%	25%	69%	16%	54%	57%	92%	72%
40-59%	73%	40%	30%	28%	30%	70%	9%	52%	57%	97%	57%
60-79%	67%	42%	33%	18%	22%	67%	9%	51%	40%	87%	27%
80-100%	63%	63%	13%	0%	0%	38%	0%	25%	25%	63%	38%

Chart 3



For signs and symptoms that correlate well with the incidence of appendicitis, there should be a linear relationship between the criterion and the surgeons estimate of the likelihood of appendicitis. Most patients without appendicitis (the 0-19% group) should have should have a preponderance of atypical signs and symptoms. Those patients in the high likelihood end of the spectrum (80-100% group) should have a very low incidence of atypical signs and symptoms. Virtually all of the signs and symptoms do not show this type of relationship, other than an elevated WBC (as depicted in the following charts).

Chart 4

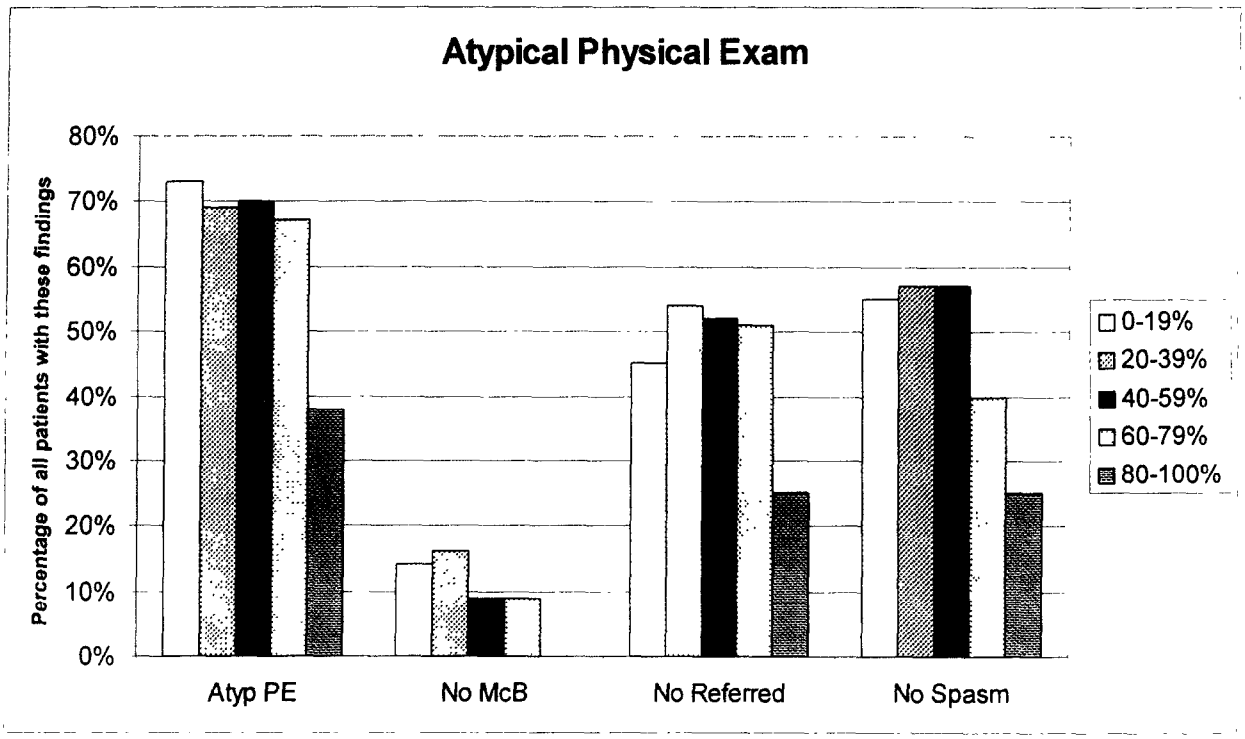
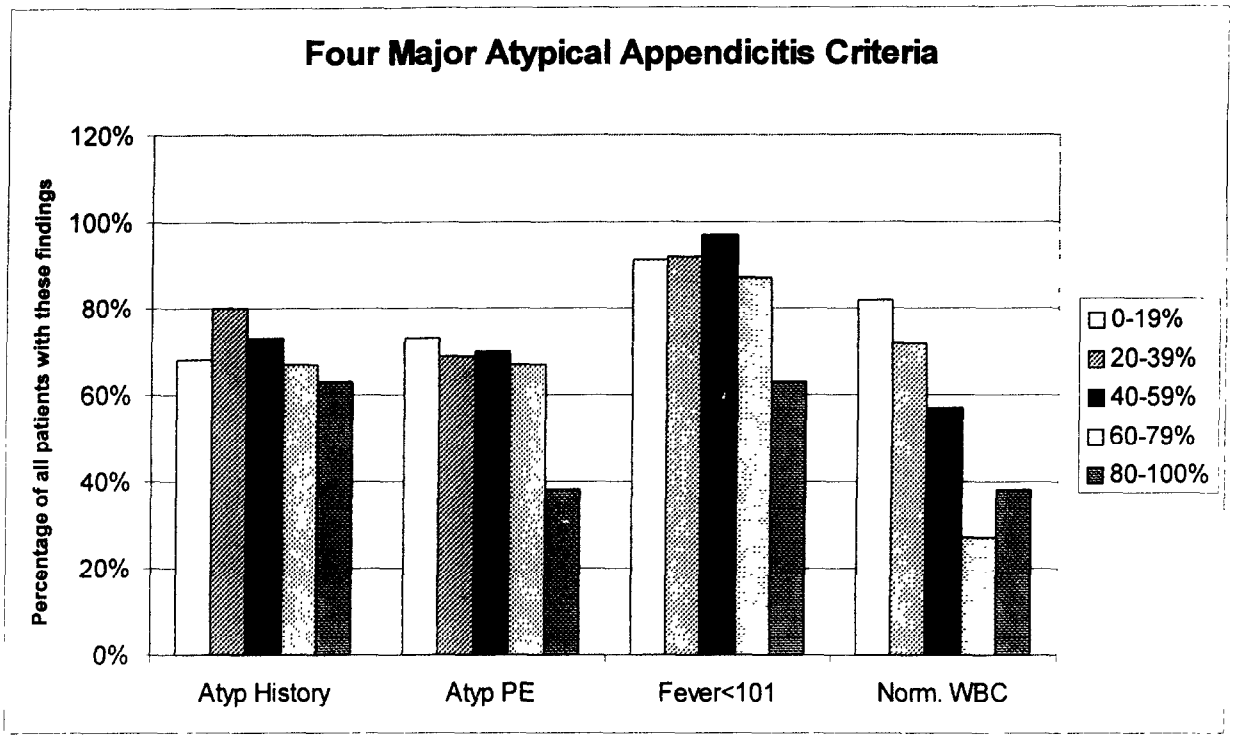


Chart 5



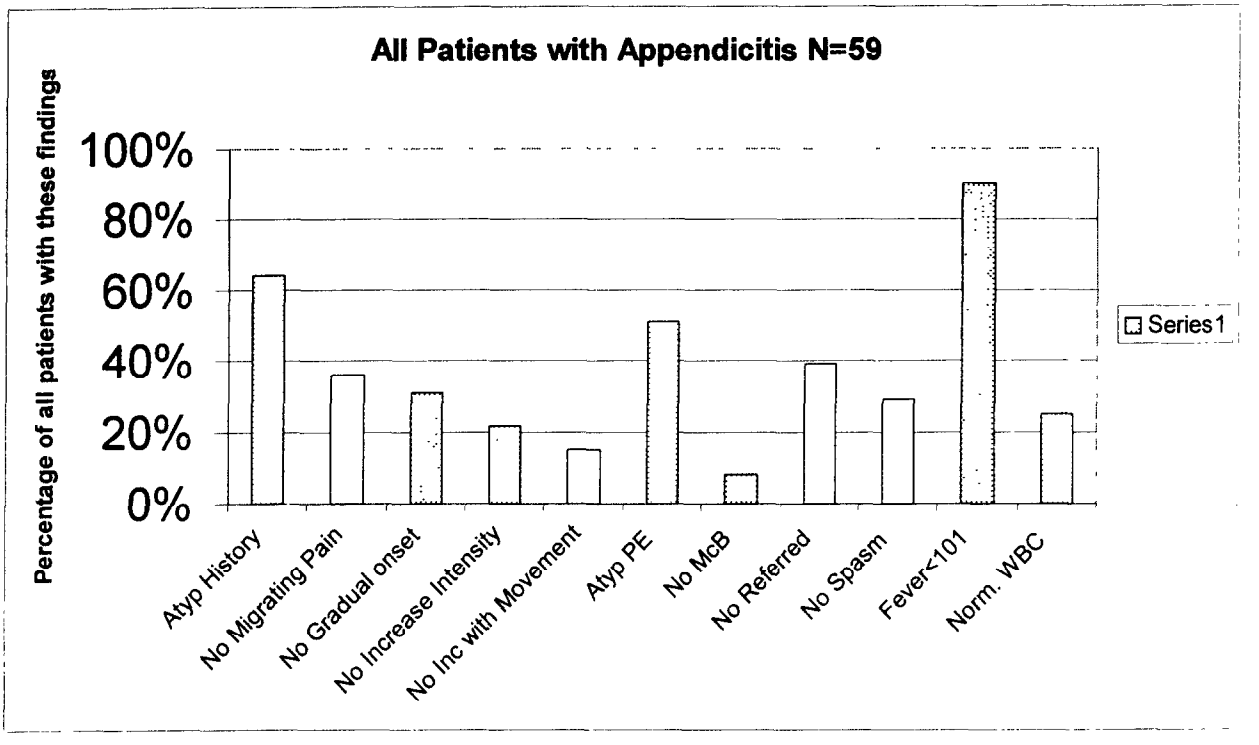
In patients who had a final institutional diagnosis of appendicitis (N=59), over 50% had one or more atypical signs and symptoms, atypical physical exam, or a fever under 101^0F. However only 25% had a normal WBC. Some individual signs and symptoms occurred with a low frequency, but the cumulative atypical history or physical exam criteria were met in over 50% of patients with documented appendicitis.

Table 22

ALL PATIENTS WITH APPENDICITIS N=59

Atyp History	No Migrating Pain	No Gradual onset	No Increase Intensity	No Inc with Movement	Atyp PE	No McB point tenderness	No Referred pain	No Spasm	Fever <101	Norm. WBC
64%	36%	31%	22%	15%	51%	8%	39%	29%	90%	25%

Chart 6



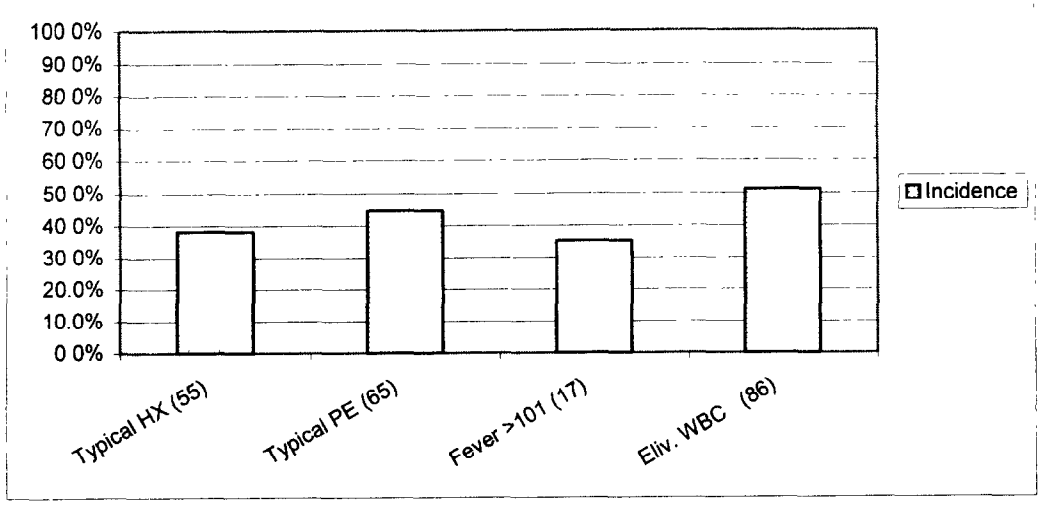
Looking at all evaluable patients and looking at those patients that did not have an atypical sign or symptom i.e. they had a typical finding for appendicitis, the incidence of appendicitis can be determined in those subgroups. In most of those subgroups, the rate of appendicitis hovers in the 30-40% range, though the incidence of appendicitis is highest in the subgroup of those with an elevated WBC count. Of the entrance criteria used in the study, the WBC was the best major criteria used. This is compared again to the surgeon's pre LeuTech scan ranking of probability of appendicitis.

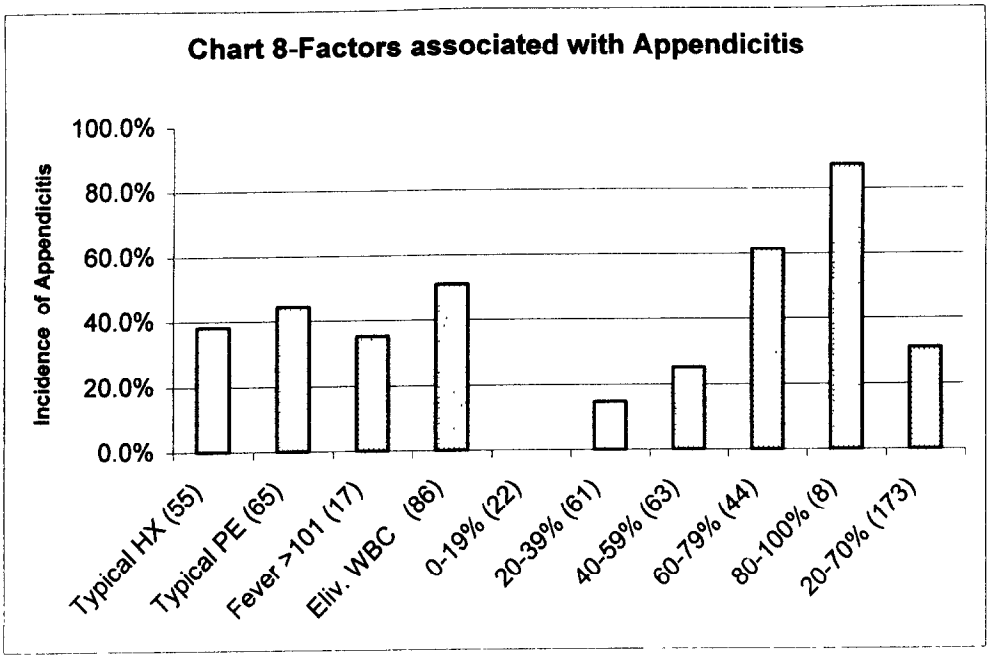
Rate of Appendicitis based on presenting Signs and Symptoms
All Evaluable Patients N=200

Table 24

	N (s)	N (a)	Incidence
Typical HX (55)	55	21	38%
Periumblical pain migrating to RLQ	99	39	39%
Gradual onset of pain	145	41	28%
Increase in intensity of Pain	148	46	31%
Pain aggravated by movement	151	50	33%
Typical PE (65)	65	29	45%
McBurney point tenderness	177	54	31%
Referred tenderness on Palp.	98	36	37%
Abd. Muscle Spasm	98	42	43%
Fever >101 (17)	17	6	35%
Eliv. WBC (86)	86	44	51%
0-19% (22)	22	0	0%
20-39% (61)	61	9	15%
40-59% (65)	65	16	25%
60-79% (44)	44	27	61%
80-100% (8)	8	7	88%
20-70% (170)	170	52	31%

Chart 7-Incidence of Appendicits





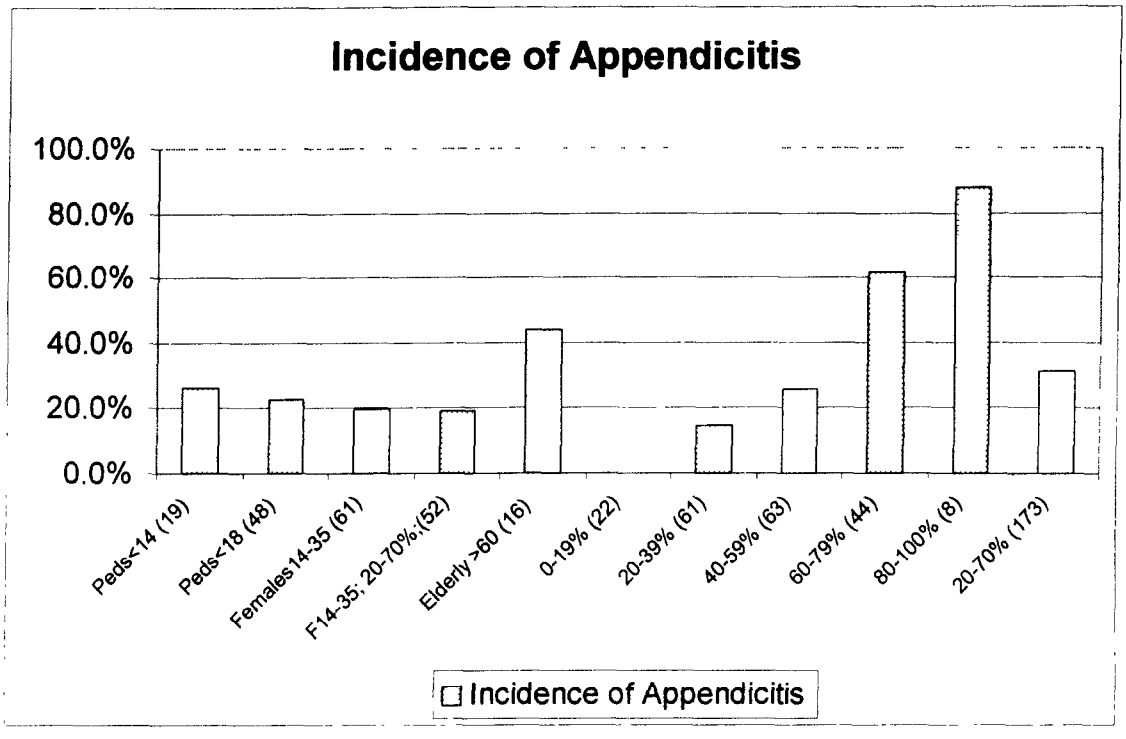
Age Subgroup Analysis

Other subgroups were identified that would perhaps represent more difficult diagnostic problems including pediatrics under the age of 14, females between the ages of 14 and 35, and the elderly (> 60). The incidence of appendicitis is displayed on the following table and chart. Of note the, the incidence of appendicitis was fairly high in the elderly population in this study. As a point of reference, the surgeon's likelihood estimates are again included.

Table 25

	Number of Patients	Incidence of Appendicitis
Peds<14 (19)	19	26%
Peds<18 (48)	48	23%
Females14-35 (61)	61	20%
F14-35; 20-70%;(52)	52	19%
Elderly >60 (16)	16	44%
0-19% (22)	22	0%
20-39% (61)	61	15%
40-59% (65)	65	25%
60-79% (44)	44	61%
80-100% (8)	8	88%
20-79%(170)	170	31%
20-70% (170)	170	31%

Chart 9


Incidence of Appendicitis
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
Peds<14 (19)
Peds<18 (48)
Females14-35 (61)
F14-35; 20-70%;(52)
Elderly >60 (16)
0-19% (22)
20-39% (61)
40-59% (63)
60-79% (44)
80-100% (8)
20-70% (173)
Incidence of Appendicitis

Following the Study design efficacy endpoints, Data were generated for each of the blinded readers, the aggregate read, and the on-site readers using all evaluable patients. Though, as will be described later, some subjects were excluded from the management decision analysis because the pre and post scan management plans were filled out by different surgeons, this did not affect this analysis. Only the pre-scan surgeon's likelihood assessment was used for this analysis. The sensitivity, specificity, accuracy, positive predictive value, negative predictive values and the likelihood ratios were calculated for each of the pre-scan probability estimates for appendicitis. Additionally subgroups of pediatric patients under the age of 14, females between the ages of 14 and 35 and patients over the age of 60 were assessed. These ages were picked to provide the largest sample sizes and capture both ends of the age population in addition to women during the higher reproductive years and greater incidence of gynecologic inflammatory conditions. Because the design of the study eliminated patients with a diagnosis of pelvic inflammatory disease (PID) as an exclusion criterion, the incidence of PID in this study is artificially low. There is insufficient data to assess the utility of this product in differentiating a patient with PID vs. appendicitis. However, this patient population as a subgroup is still important to assess due to the greater diagnostic challenge based on the anatomical differences with males.
The following tables and charts represent these data.

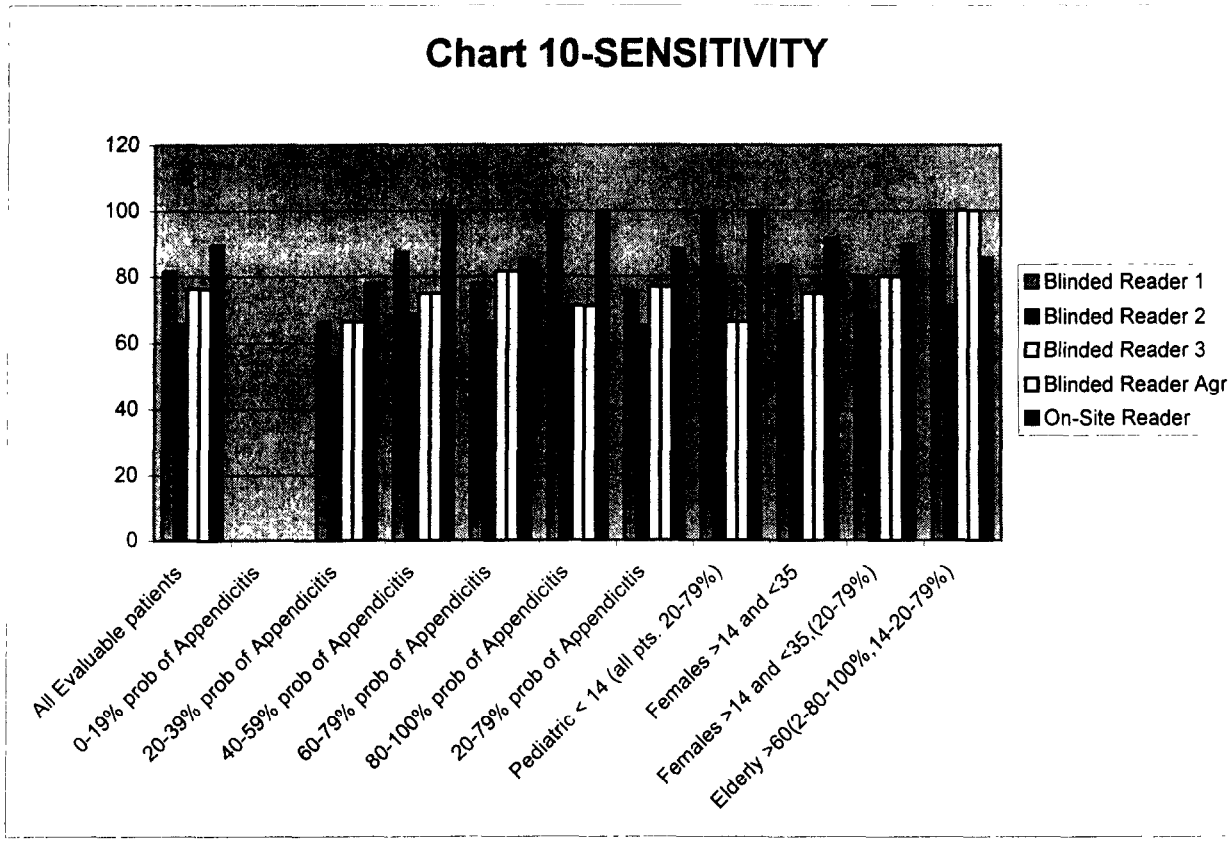


Chart 11-SPECIFICITY

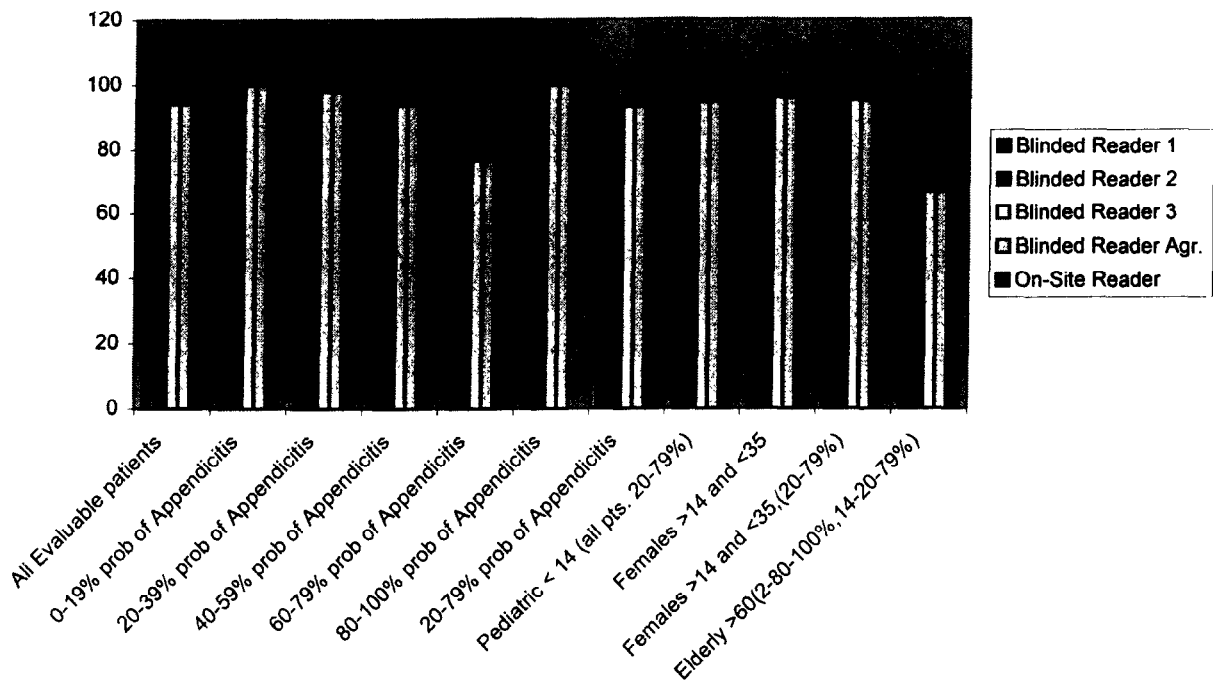


Chart 12-ACCURACY

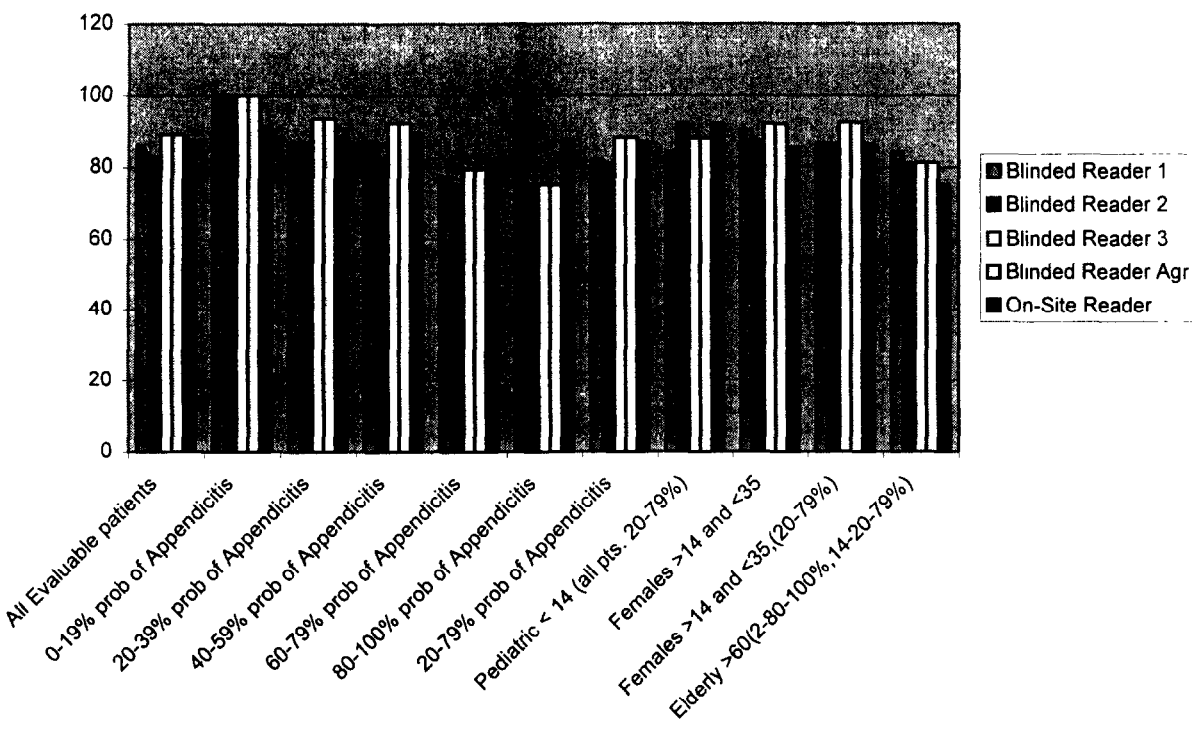


Chart 13-Positive Predictive Value

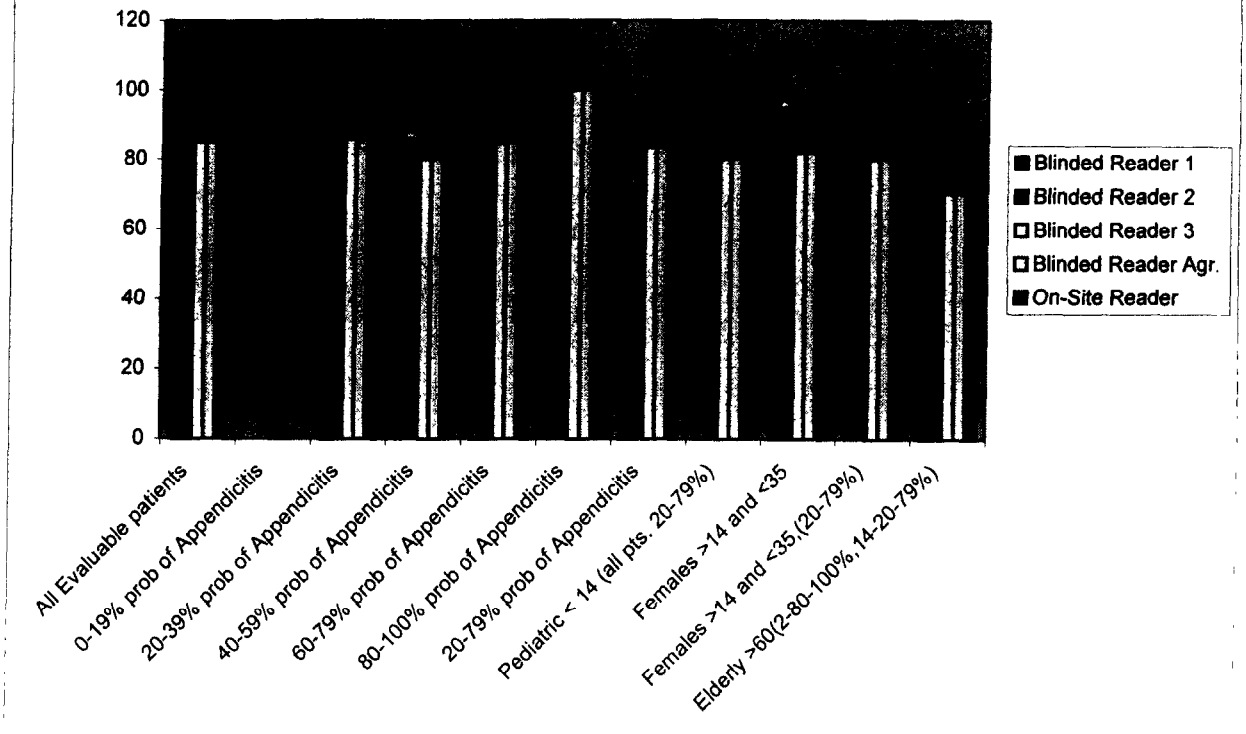


Chart 14-Negative Predictive Value

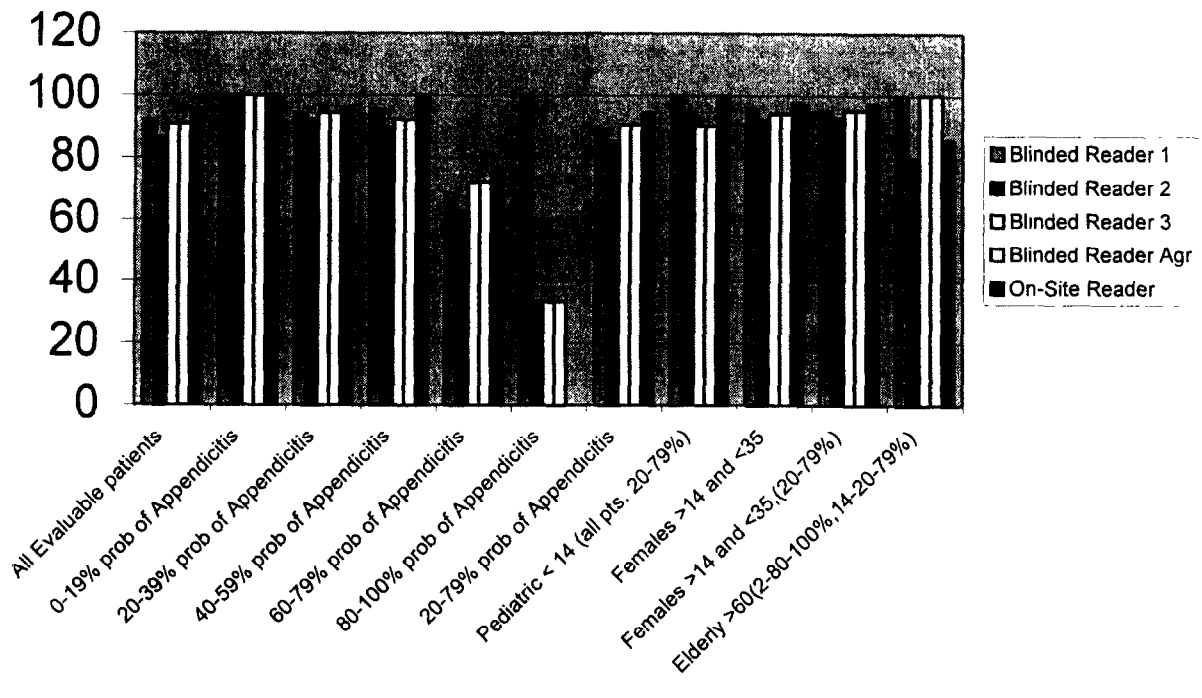


Chart 15-Positive Likelihood Ratio

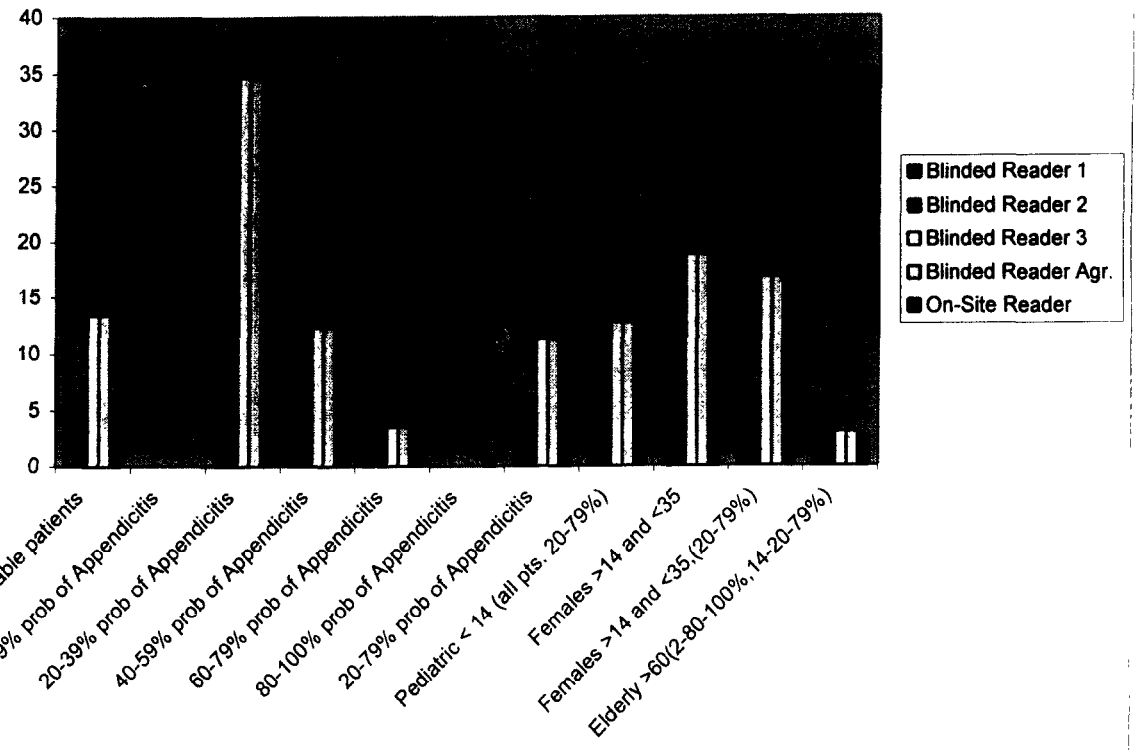
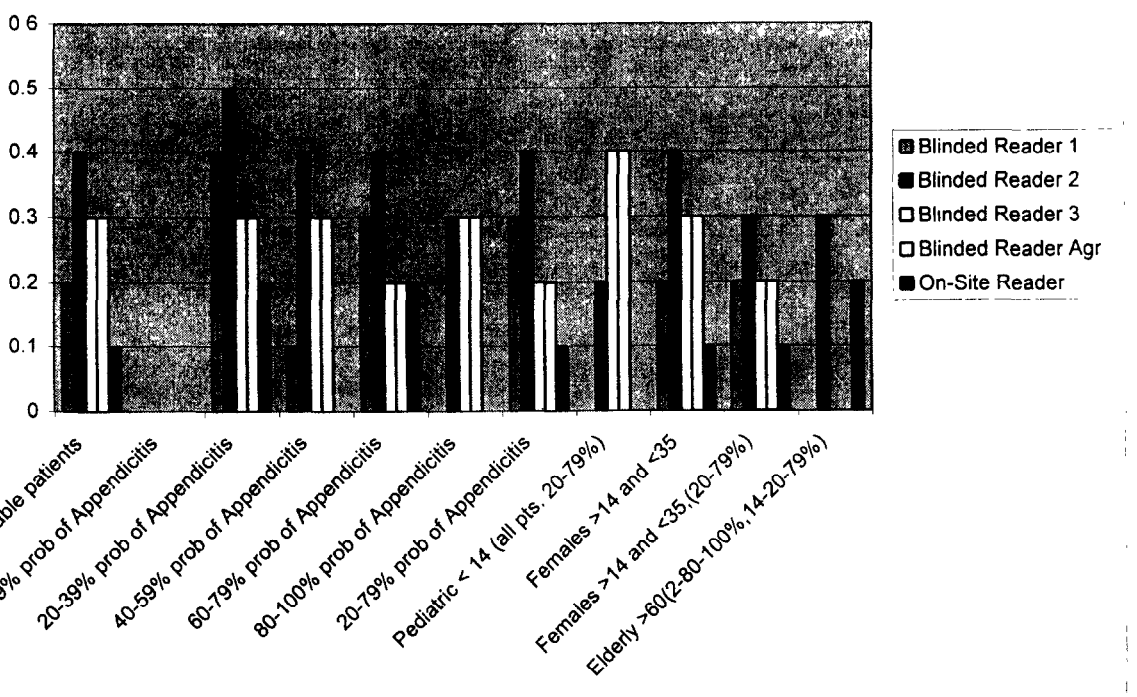


Chart 16-Negative Likelihood Ratio



3. Summary of Subgroup Analysis

Though the entrance criteria were not able to differentiate equivocal appendicitis in a consistent manner, the surgeon's management questionnaire provided an important tool to select a sub-population that could reasonably be considered equivocal. Breaking the data into the middle range of the surgeon's likelihood estimates, the 20-79% probability of appendicitis yielded efficacy outcome measures that are comparable to the study as a whole.
The women in prime reproductive years also had comparable efficacy outcome measures. These patients were selected for not having PID. As will be discussed later, the scan has a much higher rate of false positive results in patients with other infections. Therefore the accuracy of the scan in women who may have PID is not clear.
The pediatric patients were selected to be below 14y, and the scan maintained the efficacy outcome measures in this patient population.
The "geriatric" patient subgroup was chosen at > 60y to try to increase the number of patients in the group and still reflect the higher incidence of other medical problems and illnesses. Again, the efficacy outcome measures were maintained in this patient population.

F. Intended Clinical Management and Estimated Likelihood of Appendicitis

Ten patients for whom the pre- and post-Tc 99m LeuTechTm estimates were completed by different surgeons are not included in this table. An additional patient was excluded because the pre-study questionnaire was actually completed following Tc 99m LeuTechTm imaging. Bowker's test of symmetry was used to compare pre- and post-scan distributions of management scores.

The difference between pre- and post-scan score distributions was statistically significant ($p < 0.0001$), with many more shifts following the Tc 99m LeuTechTm study in the direction of correct management versus shifts in the other direction.

Prior to the Tc 99m LeuTechTm study, 29 patients whose final institutional diagnosis was acute appendicitis were to be admitted for observation. Following review of the Tc 99m LeuTechTm images, 25 of those 29 patients would have been appropriately sent to surgery, if the Tc 99m LeuTechTm images had been used in diagnosis.

No patients with a final institutional diagnosis of acute appendicitis shifted from surgery pre-scan to admit for observation or send home post-scan.

Similarly, 39 patients whose final institutional diagnosis was negative for acute appendicitis and who were to be admitted for observation prior to review of the Tc 99m LeuTechTm would have been appropriately sent home on the basis of the Tc 99m LeuTechTm study and **other clinical information** .

In addition, five patients without appendicitis who would have been sent to surgery pre-scan shifted to send home post-scan.

1. Clinical Management and Disposition

Table 26 shows the clinical management disposition of patients with and without appendicitis.

Table 26

DISTRIBUTION OF INTENDED CLINICAL MANAGEMENT DECISIONS PRIOR TO AND FOLLOWING Tc 991n LeuTechTm IMAGING, EVALUABLE PATIENTS.			
FINAL DIAGNOSIS	MANAGEMENT	Pre-LeuTechTm N	Post-LeuTechTm N
Acute Appendicitis	Send Home	5	2
	Admit for Observation	29	4
	Surgery	21	49
No Acute Appendicitis	Send Home	38	78
	Admit for Observation	84	43
	Surgery	12	13

Table 27 depicts the shifts in management of patients in this trial.

Table 27

SHIFTS IN INTENDED CLINICAL MANAGEMENT PRE- AND POST- Tc 99m LeuTechTm STUDY, EVALUABLE PATIENTS.				
	Post-Tc 99m LeuTechTm			
Pre-Tc 99m LeuTechTm	Send Home	Admit for Observation	Surgery	Pre-Total
Final Diagnosis = Acute Appendicitis				
Send Home	2	0	3	5
Admit for Observation	0	4	25	29
Surgery	0	0	21	21
Post-Total	2	4	49	55
Final Diagnosis = No Acute Appendicitis				
Send Home	34	2	2	38
Admit for Observation	39	39	6	84
Surgery	5	2	5	12
Post-Total	78	43	13	134

2. Change in Management for Pediatric Patients

- Among pediatric patients whose final diagnosis was acute appendicitis, one patient would have been sent home both prior to and following Tc 99m LeuTechTm imaging.

- Eight pediatric patients whose final institutional diagnosis was acute appendicitis;
  Four who would have been admitted for observation prior to the Tc 99m LeuTechTm imaging would have been sent to surgery following review of the images.
  Four patients would have been sent to surgery both prior to and following review of the Tc 99m LeuTechTm study.

- Thirteen pediatric patients whose final institutional diagnosis was negative for acute appendicitis;
  Ten patients who would have been admitted for observation prior to Tc 99m LeuTechTm imaging would have been sent home following review of the images.
  Two patients who would have been admitted for observation would have been sent to surgery on the basis of the Tc 99m LeuTechTm images.
  One who would have been sent home prior to Tc 99m LeuTechTm imaging would have been sent to surgery on the basis of the Tc 99m LeuTechTm images.

Table 28 shows the clinical management decisions for the pediatric population.

Table 28

PEDIATRIC DATA: DISTRIBUTION OF INTENDED CLINICAL MANAGEMENT DECISIONS PRIOR TO AND FOLLOWING Tc 99m LeuTechTm IMAGING, EVALUABLE PATIENTS.

FINAL DIAGNOSIS	MANAGEMENT	Pre-LeuTechTm N	Post-LeuTechTm N
Acute Appendicitis	Send Home	1	1
	Admit for Observation	4	0
	Surgery	4	8
No Acute Appendicitis	Send Home	14	23
	Admit for Observation	22	10
	Surgery	0	3

Table 29 depicts the shifts in management for the pediatric patients.

Table29

PEDIATRIC DATA: SHIFTS IN INTENDED CLINICAL MANAGEMENT PRE- AND POST-Tc 99m LeuTechTm, STUDY, EVALUABLE PATIENTS.				
	Post-Tc 99m LeuTechTm			
Pre-Tc 99m LeuTechTm	Send Home	Admit for Observation	Surgery	T-Pre-Total
Final Diagnosis = Acute Appendicitis				
Send Home	1	0	0	1
Admit for Observation	0	0	4	4
Surgery	0	0	4	4
Post-Total	1	0	8	9
Final Diagnosis = No Acute Appendicitis				
Send Home	13	0	1	14
Admit for Observation	10	10	2	22
Surgery	0	0	0	0
Post-Total	23	10	3	36

3. Surgical likelihood estimates

Table 30 shows the shift in the surgeons estimation of the likelihood of appendicitis both before and after the scan, based on the surgeon's management questionnaire.

Table 30

DISTRIBUTION OF ESTIMATES OF LIKELIHOOD* OF APPENDICITIS PRE- AND POST-Tc 99m LeuTechTm STUDY.

	Post-Tc 99m LeuTechTm Study					
Pre-Tc 99m LeuTechTm Study	0-19%	20-39%	40-59%	60-79%	80-100%	Pre-Total
Final Diagnosis = Acute Appendicitis						
0-19%	0	0	0	0	0	0
20-39%	3	1	1	1	3	9
40-59%	0	0	0	5	10	15
60-79%	0	1	0	7	16	24
80-100%	0	0	0	0	7	7
Post-Total	3	2	1	13	36	55
Final Diagnosis No Acute Appendicitis						
0-19%	20	1	0	1	0	22
20-39%	33	13	2	1	0	49
40-59%	24	10	7	4	0	45
60-79%	6	5	1	2	3	17
80-100%	0	0	0	1	0	1
Post-Total	83	29	10	9	3	134

0 - 19% = Almost definitely not appendicitis;
20 - 39% = Probably not appendicitis;
40 - 59% = Indeterminate appendicitis;
60 - 79% = Probably appendicitis
80 - 100% = Almost definitely appendicitis.

H. ROC Analysis

- ROC analysis was performed to compare the ROC curves pre- and post-Tc 99m LeuTechTm. The difference between the diagnostic performance pre- and post-scan was tested with the univariate z-score test, which compares the areas under the respective curves.

- The ROC curves depict the relationship between a diagnostic procedure's performance and the likelihood or confidence threshold that an observer or reader uses to call a patient positive.

- The post-scan curve is superior to the pre-scan curve, with the difference between the areas under the curves highly statistically significant, $p < 0.0001$.

- For any given false positive fraction [FPF = FP/N (-)], the post-scan true positive fraction [TPF = TP/N (+)] is always greater than the pre-scan TPF, while for any given TPF, the post-scan FPF is always less than the pre-scan FPF.

- The post-scan curve indicates that a likelihood threshold of 60 - 79% would be associated with sensitivity of 86% and specificity of 90% (corresponding observed values 89% and 91%); while at the 40 - 59% threshold, sensitivity and specificity would be 90% and 83%, respectively (corresponding observed values 91% and 84%).

I. Summary:

- LeuTech maintains reasonable sensitivity and specificity for both blinded readers and onsite readers. Of note, the specificity is higher than the sensitivity for the blinded readers. The reverse of this is true for the onsite readers.
- Isolating subgroups of patients, based on the surgeon's likelihood estimate of appendicitis to better assess the "atypical" population of patients, did not significantly affect the overall parameters of efficacy.
- Isolating pediatric patients, elderly patients and female patients during the major child bearing years also did not affect the efficacy outcomes

Section IV – Pooled Data

A. Pooled Phase 2 and Phase 3 Results:

1. Introduction:

Both the phase two and phase three trials were conducted under similar protocols. They used the same LeuTech dose. Both protocols sought to enroll patients with atypical signs and symptoms of appendicitis, though the phase II study had a 50% rate fore appendicitis in enrolled patients. The phase III study had a 30% rate for appendicitis. The efficacy endpoints were also similar between the two studies. Both studies had blinded readers provide the primary efficacy endpoints.

Data was therefore pooled for the two studies. Since the blinded readers were different in the two studies, the aggregate blinded reads were used for the primary assessment. As per the sponsor, for each of the efficacy measurements, a weighted pooled estimate was obtained based on the method described by Fleiss for combining data across studies.

$P_{pooled} = \frac{w_2P_2 + w_3P_3}{w_2 + w_3}$ P_2= diagnostic measure phase II

P_3= diagnostic measure phase III

w_2 and w_3 are there associated weights provided by the inverse of the measure's variance.

B. Demographic Characteristics:

The demographic information is presented in the next two tables. Both studies had similar profiles.

Summary Statistics for Age, Weight, Height and BMI, Studies 98-004 and 97-003

Table 1

	N	MIN.	MAX.	MEAN	I STD.DEV.
AGE (yr.)	259	5.2	85.9	30.2	16.03
WEIGHT (kg)	259	21.4	127.3	68.5	20.24
HEIGHT (cm)	257	104.1	198.1	164.7	14.38
BMI	257	12.6	46.7	24.9	5.60

Distribution of Gender and Race, Studies 98-004 and 97-003

Table 2

		N	%
GENDER	Female	52	59
	Male	107	41
	TOTAL	**259**	**100**
RACE	White	171	66
	Hispanic	60	23
	Black	19	7
	Other	9	4
	TOTAL	**259**	**100**

1. Atypical signs and symptoms:

The distribution of atypical signs and symptoms was also similar between the two studies.

Distribution of Signs and Symptoms Comprising Equivocal Presentation, Studies 98-004 and 97-003

Table 3

CRITERIA	N *	%
Atypical history/symptoms	182	70
Atypical physical examination	156	60
Fever less than 101' F	229	88
WBC count < 10,500/MM3 or within normal range	136	53
TOTAL	259	
*Sum of the Ns exceeds the number of patients because some patients had more than one equivocal sign or symptom.		

2. Final Institutional Diagnosis:

The final institutional diagnosis for appendicitis was skewed to the rate observed in the phase III trial only because of the greater number of patients.

Distribution of Final Institutional Diagnosis for Appendicitis/No Appendicitis and Infection/No Infection, Evaluable Patients, Studies 98-004 and 97-003

Table 4

	POSITIVE N (%)	NEGATIVE N (%)
Diagnosis for Acute Appendicitis	87 (34)	169 (66)
Diagnosis for Infection'	117 (46)	139(54)
' Three patients had both acute appendicitis and other infection.		

C. Efficacy:

The efficacy evaluation of the pooled data compares the aggregate blinded readers and the pooled onsite investigators. The data is again skewed to the larger phase III trial. The sensitivity is greater for the onsite investigators, and the specificity is greater for the aggregate blind readers. The onsite readers have much more clinical information than do the offsite readers.

Sensitivity, Specificity, Accuracy, PPV and NPV of Blinded Readers' Evaluations of Tc 99m LeuTechTm Images for Appendicitis/No Appendicitis, Evaluable Patients, Studies 98-004 and 97-003

Table 5

SENSITIVITY				
EVALUATION	N(+)	TP	Sensitivity	95% Lower Limit
Blind-Read Aggregate	87	69	82	73
Site Investigators	82	76	93	86
SPECIFICITY				
EVALUATION	N(-)	TN	Specificity	95% Lower Limit
Blind-Read Aggregate	169	150	92	87
Site Investigators	156	132	85	79
ACCURACY				
EVALUATION	NT	TP	Accuracy	95% Lower Limit
Blind-Read Aggregate	256	219	86	82
Site Investigators	238	208	87	83
PPV				
EVALUATION	TP +FP	TP	PPV	95% Lower Limit
Blind-Read Aggregate	88	69	79	70
Site Investigators	100	76	76	68
NPV				
EVALUATION	TN + FN	TN	NPV	95% Lower Limit
Blind-Read Aggregate	168	150	89	85
Site Investigators	138	132	96	91

N (+) is the number of patients positive for acute appendicitis by final institutional diagnosis.
N (-) is the number of patients negative for acute appendicitis by final institutional diagnosis.
NT is the total number of patients.
'Blind-read aggregate estimates based on weighted 98-004 and 97-003 estimates.

1. Likelihood Ratios: Appendicitis

The likelihood ratios are similar in the pooled data to those in the phase III trial.

Likelihood Ratios of Tc 99m LeuTechTm Images For Appendicitis/No-Appendicitis, Evaluable Patients, Studies 98-004 and 97-003

Table 6

EVALUATION	LR(+)	95% Confidence Interval	LR(-)	95% Confidence Interval
Blind-Read Aggregate	5.03	3.34-7.60	0.25	0.17-0.38
Site Investigators	6.02	4.15-8.75	0.09	0.04-0.19
[1]Estimates based on weighted 98-004 and 97-003 estimates.				

B. Management:

The management of patients is reflected in the questionnaires that were filled out both before and after the LeuTech scan. In the pooled data, two patients would have been sent home after the scan. One patient was a true positive, but the sheet was filled out that the patient would have been sent home. The second was a false negative, and the patient underwent an appendectomy based on clinical findings. There was a clear shift in a positive direction in patient management as reflected in table 10.

1. Clinical Management Disposition

Distribution of Intended Clinical Management Decisions Prior to and Following Tc 99m LeuTechTm Imaging, Evaluable Patients, Studies 98-004 and 97-003

Table 9

FINAL DIAGNOSIS	MANAGEMENT	Pre-LeuTechTm	Post-LeuTechTm
Acute Appendicitis	Send Home	7	2
	Admit for Observation	47	7
	Surgery	29	74
No Acute Appendicitis	Send Home	42	97
	Admit for Observation	104	49
	Surgery	16	16

2. Shift in Clinical Management

Shifts in Intended Clinical Management Pre- and Post-Tc 99m LeuTechTm Imaging, Evaluable Patients, Studies 98-004 and 97-003

Table 10

Pre-Tc 99m LeuTechTm	Post-Tc 99m LeuTechTm			
	Send Home	Admit for Observation	Surgery	Pre-Total
Final Diagnosis = Acute Appendicitis				
Send Home	2	0	5	7
Admit for Observation	0	7	40	47
Surgery	0	0	29	29
Post-Total	2	7	74	83
Final Diagnosis = No Acute Appendicitis				
Send Home	38	2	2	42
Admit for Observation	52	45	7	104
Surgery	7	2	7	16
Post-Total	97	49	16	162

3. Likelihood of Appendicitis estimates:

Though overall there was a positive shift in the estimate of those with appendicitis and those without appendicitis, 3 patients with a final diagnosis of acute appendicitis shifted from a 20-39% chance pre scan to a 0-19% chance post-scan. Additionally, 3 patients without appendicitis shifted to a high probability of appendicitis after their LeuTech scan.

Distribution of Estimates of Likelihood of Appendicitis Pre- and Post-Tc 99m LeuTechTm Evaluable Patients, Studies 98-004 and 97-003'

Table 11

	Post-Tc 99m LeuTechTm Study					
Pre-Tc 99m LeuTechTm Study	0-19%	20-39%	40-59%	60-79%	80-100%	Pre-Total
Final Diagnosis = Acute Appendicitis						
0-19%	0	0	0	0	0	**0**
20-39%	3	1	1	2	6	13
40-59%	0	0	0	5	11	16
60-79%	0	1	0	9	20	30
80-100%	0	0	0	0	8	8
Post-Total	**3**	2	1	16	45	67
Final Diagnosis = No Acute Appendicitis						
0-19%	21	1	0	1	0	23
20-39%	35	13	2	1	0	51
40-59%	28	10	9	6	0	53
60-79%	7	5	1	3	3	19
80-100%	0	0	0	1	0	1
Post-Total	91	29	12	12	3	147

0 -19% = Almost definitely not appendicitis
20 - 39% = Probably not appendicitis
40 - 59% = Indeterminate appendicitis
60 - 79% = Probably appendicitis
80 - 100% = Almost definitely appendicitis

E. Subgroup Analysis:

1. Age groups:

Pooling the data from the phase II and phase III trials allows the evaluation of a greater number of pediatric and geriatric patients under the same general trial design. A total of 63 patients from 5-17 and 12 patients over the age of 65 are represented. There were no statistically significant differences between these subgroups, and the main 18-64 age group.

Table 13 shows the pooled data for the various age groups.

Comparison Of Age Subgroups: 5 - 17, 18 - 64, >65 Years, Evaluable Patients, Studies 98-004 and 97-003

Table 13

SENSITIVITY											
	5 - 17 yr.			18 - 64 yr.			>65 yr.			Chi	Sig.
	N(+)	TP	Sens.	N(+)	TP	Sens.	N	TP	Sens(b)	Squ	Prob.
Blind-Read Aggregate'	20	17	73	61	46	76.1	6	6	100	2.155	0.340
Site Investigators	19	18	95	57	53	93.0	6	5	83	0.829	0.660
SPECIFICITY											
	5 - 17 yr.			18 - 64 yr.			> 65 yr.			Chi	Sig.
	N(-)	TN	Spec.	N(-)	TN	Spec	N(-)	TN	Spec(c)	Squ	Prob.
Blind-Read Aggregate	43	40	94	120	105	91.1	6	5	83	1.549	0.460
Site Investigators	41	37	90	109	90	82.6	6	5	83	1.246	0.536

N (+) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N (-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis.
'Blind-read aggregate estimates based on weighted 98-004 and 97-003 estimates.
b Unweighted average based on sensitivities of 2/2 and 4/4 for Phase 2 and 3, respectively.
c Result based on Phase 3 study, 98-004, only; no Phase 2 patients in this age subgroup had a negative final institutional diagnosis.

2. Gender:

No differences were noted between genders in the pooled data. These data did not separate out women in their primary reproductive years as was done earlier.

Comparison of Gender Subgroups, Evaluable Patients, Studies 98-004 and 97-003

Table 14

SENSITIVITY								
	MALE			FEMALE			x 2	Sig. Prob.
	N(+)	TP	**Sensitivity**	N(+)	TP	**Sensitivity**		
Blind-Read Aggregate	42	31	81	45	38	85	1.412	0.234
Site Investigators	40	37	93	42	39	93	0.001	0.976
SPECIFICITY								
	MALE			FEMALE			x 2	Sig. Prob.
	N(-)	TN	Specificity	N(-)	TN	**Specificity**		
Blind-Read Aggregate	62	54	87	107	96	95	0.096	0.756
Site Investigators	58	48	83	98	84	86	0.193	0.660

N(,) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N(-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis.
a Blind-read aggregate estimates based on weighted 98-004 and 97-003 estimates.

3. Race:

No significant differences were noted between races, though this was broken down between whites, and non-whites only.

Comparison of Race Subgroups, Evaluable Patients, Studies 98-004 and 97-003

Table 15

SENSITIVITY								
	WHITE			ALL OTHER			x 2	Sig. Prob.
	N(+)	TP	Sensitivity	N(+)	TP	Sensitivity		
Blind-Read Aggregate	53	38	72	34	31	80	2.938	0.086
Site Investigators	50	44	88	32	32	100	3.333	0.067
SPECIFICITY								
	WHITE			ALL OTHER			x 2	Sig. Prob.
	N(-)	TN	Specificity	N(-)	TN	Specificity		
Blind-Read Aggregate	116	104	92	53	46	90	0.078	0.780
Site Investigators	106	89	84	50	43	86	0.299	0.584

N(,) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N(-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis.
[a]Blind-read aggregate estimates based on weighted 98-004 and 97-003 estimates.

4. Weight (BMI):

Though there were again no significant differences between the groups, there was a falling off of both the sensitivity and specificity for the onsite readers that was not noted for the blinded readers.

Comparison of BMI Subgroups, Evaluable Patients, Studies 98-004 and 97-003

Table 16

SENSITIVITY								
	BMI < 27			BMI ≥27			x 2	Sig. Prob.
	N(+)	TP	**Sensitivity**	N(+)	TP	**Sensitivity**		
Blind-Read Aggregate'	62	49	80	23	18	78	0.014	0.906
Site Investigators	59	56	95	21	18	86	2.008	0.156
SPECIFICITY								
	BMI < 27			BMI ≥ 27			x 2	Sig. Prob.
	N(-)	TN	**Specificity**	N(-)	TN	**Specificity**		
Blind-Read Aggregate	116	103	90	53	47	94	0.017	0.896
Site Investigators	105	92	88	51	40	78	2.344	0.125

N(+) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N(-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis.
a Blind-read aggregate estimates based on weighted 98-004 and 97-003 estimates.

5. Pediatric:

Pooling the data allows for a breakdown of the pediatric patients into 5-9 yr. old and 10-17 yr. old. Even with the pooled data, there were only 15 patients in the 5-9 yr. old age group. The 10-17 yr. old group has 48 patients. The efficacy parameters are similar for the pediatric subgroups compared to the study as a whole.

Pediatric Subgroups

Sensitivity, Specificity, Accuracy, PPV and NPV for evaluable Patients Studies 98-004 and 97-003

Table 17 (sponsor)

SENSITIVITY						
	5 - 9 y			10- 17 y		
	N(+)	TP	Sensitivity	N(+)	TP	Sensitivity
Blind-Read Aggregate[1]	7	6	86	13	11	85
Site Investigators	7	7	100	12	11	92
SPECIFICITY						
	5 - 9 y			10- 17 y		
	N(-)	TN	Specificity	N(-)	TN	Specificity
Blind-Read Aggregate	8	8	100	35	32	92
Site Investigators	7	7	100	34	30	88
ACCURACY						
	5 - 9 y			10 - 17 y		
	NT	TN+TP	Accuracy	NT	TN+TP	Accuracy
Blind-Read Aggregate	15	14	92	48	43	90
Site Investigators	14	14	100	46	41	89
PPV						
	5 - 9 y			10 - 17 y		
	TP+FP	TP	PPV	TP+FP	TP	PPV
Blind-Read Aggregate	6	6	100	14	11	82
Site Investigators	7	7	100	15	11	73
NPV						
	5 - 9 y			10- 7 y		
	TN+FN	TN	NPV	TN+FN	TN	NPV
Blind-Read Aggregate	9	8	89	34	32	93
Site Investigators	7	7	100	31	30	97

N (+) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis.
N (-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis.
[1] Blind-read aggregate estimates based on weighted 98-004 and 97-003 estimates.

a. Pediatric Management:

As was noted in the phase III study there was a positive shift in the management of the pediatric patients as evaluated by the management questionnaire. One false negative scan is represented in the 10-17 yr. old group as a patient that would have been sent home both prior to and after the LeuTech scan.

Shifts In Intended Clinical Management Pre- and Post-Tc 99m LeuTechTm Study For, Evaluable Patients, Studies 98-004 and 97-003

Table 18

FINAL DIAGNOSIS = ACUTE APPENDICITIS				
	Post-Tc 99m LeuTechTm			
Pre-Tc 99m LeuTechTm	Send Home	Admit for Observation	Surgery	Pre-Total
5-9YR				
Send Home	0	0	1	1
Admit for Observation	0	0	3	3
Surgery	0	0	2	2
Post-Total	0	0	6	6
10 - 17 YR				
Send Home	1	0	0	1
Admit for Observation	0	0	8	8
Surgery	0	0	3	3
Post-Total	1	0		12
FINAL DIAGNOSIS NO ACUTE APPENDICITIS				
	Post-Tc 99m LeuTechTm			
Pre-Tc 99m LeuTechTm	Send Home	Admit for Observation	Surgery	Pre-Total
5-9YR				
Send Home	3	0	0	3
Admit for Observation	1	4	0	5
Surgery	0	0	0	0
Post-Total	4	4	0	8
10 - 17 YR				
Send Home	I 1	0	1	12
Admit for Observation	12	7	2	21
Surgery	1	0	0	1
Post-Total	24	7	3	34

6. Antibiotics:

A comparison is made between those patients on antibiotics, and those who were not on antibiotics. A statistically significant difference is noted in the specificity of the test This is true for both the onsite readers, who had a lower specificity to start with, and the blinded readers. A detailed explanation by the sponsor is included after the table, with some additional commentary added.

Comparison of Antibiotic Use Subgroups, Evaluable Patients, Study 98-004 and 97-003

Table 18

SENSITIVITY								
	ANTIBIOTICS			**NO ANTIBIOTICS**			X2	Sig. Prob.
	N(+)	TP	**Sensitivity**	N(+)	TP	**Sensitivity**		
Blind-Read Aggregate	12	11	89	75	58	80	1.492	0.222
Site Investigators	12	11	92	70	65	93	0.005	0.944
SPECIFICITY								
	ANTIBIOTICS			**NO ANTIBIOTICS**			X2	Sig. Prob.
	N(-)	TN	**Specificity**	N(-)	TN	**Specificity**		
Blind-Read Aggregate	24	19	80	145	131	94	4.734	**0.029**
Site Investigators	22	15	68	134	117	87	5.938	**0.014**
N(+) is the number of patients diagnosed as positive for acute appendicitis by final institutional diagnosis N(-) is the number of patients diagnosed as negative for acute appendicitis by final institutional diagnosis. 'Blind-read aggregate estimates based on weighted 98-004 and 97-003 estimates.								

- Sensitivity for subgroups according to antibiotic usage was comparable
- Specificity was significantly higher ($p < 0.05$) for patients not taking antibiotics, both for the aggregate blind-read results (13% higher) and for the site investigators (19% higher).
- Prevalence of appendicitis was the same (about one third of patients) for patients taking antibiotics and for patients not taking antibiotics.
- The prevalence of other infections was three times higher for patients taking antibiotics. The numbers are shown below:

Final Diagnosis	Antibiotic Users		Non-Users	
Acute Appendicitis	12	(33%)	75	(34%)
Other Infection	10	(28%)	20	(9%)
Negative	14	(39%)	125	(57%)
Total	36		222	

- The rate of false-positive findings for appendicitis was generally higher among patients who had other infections:
- 43% of other infections (13 cases) were read as false positive for appendicitis by the blind-read aggregate
- 31% of other infections (9 cases) were read as false positive for appendicitis by the site investigators.
- 4% of negative patients being read as false positive by the blind read aggregate
- 12% of negative patients being read as false positive by the site investigators.
- False-positive findings for appendicitis among patients with other infections were similar whether patients were taking antibiotics or not.
- The higher proportion of other infections among antibiotic users made it appear as if a higher false positive rate occurred for this group.
- Differences in specificity are not a result of a drug interaction, per se, but rather the result of the higher prevalence of other infections among patients being treated with antibiotics.

Comments: These numbers, as presented by the sponsor, are based on a very small sample size. Additionally, the use of antibiotics was not well characterized especially with regard to the timing of their administration. Medication was recorded if it was given 24 hrs. or less prior to the scan or after the scan. There does not appear to be an acute interaction between the use of antibiotics and the performance of the scan. However, the relationship between the incidence of false positive results and other infections provides a cautionary note when interpreting the results of a positive scan for appendicitis.

- Only 26 patients in the phase III study had other infections, of which 3 also had appendicitis. This leaves 23 patients to assess for other infections. 4 of these patients were given antibiotics around the time of the scan. All 4 of those patients had false positive scans by the blind aggregate read.
- Of the remaining 174 patients without other infections, 21 received antibiotics, and none of these had a FP reading for appendicitis.
- 10 FP reads by the blind aggregate in the phase III trial were in patients with other infections.
- There were 7 patients with other infections in the phase II study. Only one patient received antibiotics around the time of the scan and that patient was read as a true negative by the blind aggregate read.

Study 95-001

A phase I/II open-label within patient comparative study of patients with suspected infectious processes, 29 of whom have had appendicitis. This is a study that is not directly comparable to the phase II and III trials, as patients with any infectious process are enrolled, not just patients with suspected appendicitis. Of the 29 patients with a diagnosis of appendicitis, and based on final institutional diagnosis as truth;

- Accuracy using Tc 99m LeuTechTm images was 79% of patients (23 of 29).
- Sensitivity of Tc 99m LeuTechTm images was 88% (14 of 16 patients)
- Specificity of Tc 99m LeuTechTm images was 69% (9 of 13 patients).

Though the numbers are small, these data are in closer agreement with the phase II results and the onsite investigators with a higher sensitivity, and a dramatically lower specificity.

Agreement between Tc 99m LeuTechTm Results and Final Institutional Diagnosis

Table 12

Final Institutional Diagnosis	**Tc 99m LeuTechTm Diagnosis**		**TOTAL**
	Negative for Acute Appendicitis	**Positive for Acute Appendicitis**	
Negative for Acute Appendicitis	9	4	**13**
Positive for Acute Appendicitis	2	14	**16**
TOTAL	**11**	**18**	29

Section V -Safety Data

A. HAMA Evaluation:

HAMA response was evaluated in Study 97-001 (clinical pharmacology, 30 normal volunteers). Under Palatin BB-IND 7358, HAMA response was evaluated in 20 patients enrolled in Study 98-004 (Phase 3 appendicitis). Blood samples were obtained prior to injection of Tc 99m LeuTechTm and at 3 to 4 weeks post-injection. Subjects in Studies 97-001 were re-tested at 3-4 months for HAMA response. Patients in Study 98-004 who had a positive response at 3-4 weeks were to be re-tested for HAMA response at 12-16 weeks post-injection.

No subjects had a positive HAMA response at any time point tested.

The Gratz-Becker study also evaluated HAMA response and the results are reported in the literature, but no individual subject data were available. As reported, blood samples were drawn in all 17 patients prior to dosing and at 3 months post-dosing in 14 patients. One patient had a high HAMA level before injection and blood samples at 3 months post-dosing were not available in the remaining 2 patients. The Gratz publication states that, with the ELISA for HAMA in serum, no HAMA formation was detectable at 3 months after injection.

Table 1

Study and Site	3 - 4 Weeks	12 - 16 Weeks
	Proportion Positive (%)	**Proportion Positive** (%)
Study 97-001	0/30(0.0)	0/30(0.0)
Study 98-004 *	0/20(0.0)	-
Study 95-001	0/4(0.0)	0/4(0.0)
All	0/54(0.0)	0/34(0.0)

*Patients who had a positive response at 3-4 weeks were to be re-tested for HAMA response at 12-16 weeks post-injection, however; none had to be re-tested.

B. Summary of Adverse Events Phase III:

Seventeen of 203 patients injected with Tc 99m LeuTechTm reported one or more adverse events, for a total of 24 adverse events. Twenty of the 24 events were rated as mild in intensity and four were considered moderate in intensity. There were no severe or serious adverse events. The time of onset relative to the injection ranged from 0 to 104 minutes and the duration ranged from 1 minute to 70 minutes, with the exception of an episode of headache that was reported as continuous from the day following the injection to the 2-week follow-up. Action was taken for three events; each involved a change of position to resolve the event. All events except the continuous headache had resolved by the end of the study period, which was two hours post-injection or the time of discharge or surgery, whichever came first.

The safety data provided by the sponsor are broken down into the types of adverse events experienced, the distribution of the adverse events, a summary of laboratory findings, and a summary of vital sign findings post injection. There are many changes that reached statistical significance but are not felt to have clinical significance.

Individual changes in vital signs and laboratory measurements that were considered to be clinically significant are also presented.

Conclusions are made at the end of these individual changes.

Additional data are presented from the pooling of experiences with the product, and no new safety concerns are identified.

2. **Patient adverse Events**

Table 2 lists the 24 adverse events recorded in the phase III trial.
Table 3, the distribution of patients experiencing an adverse event.

Table 2

ADVERSE EVENTS FOLLOWING ADMINISTRATION OF Tc 99m LeuTechTm.						
PT	EVENT (COSTART)	INTENSITY	MIN. POST INJECTION	DURATION (MIN.)	RELATED TO DRUG	ACTION TAKEN
A-18	DYSPNEA	Mild	3	5	No	None
A-21	SYNCOPE	Mild	80	1	No	Placed Supine
A-32	SYNCOPE	Mild	57	1	No	None
B-02	PAIN CHEST	Mild	7	9	Possibly	None
	VASODILATATION	Mild	6	5	Probably	None
C-01	HEADACHE	Moderate	4	15	Possibly	None
	VASODILATATION	Mild	4	15	Possibly	None
E-21	PAIN INJECT SITE	Mild	1	70	Probably	None
	INJECT SITE REACT	Mild	1	70	Probably	None
F-01	DIZZINESS	Mild	0	5	Possibly	None
	DYSPNEA	Mild	0	5	Possibly	None
F-02	VASODILATATION	Mild	8	10	Possibly	None
F-03	VASODILATATION	Moderate	4	5	Possibly	None
	DYSPNEA	Mild	4	5	Possibly	None
G-02	HEADACHE	Moderate	940	Unknown'	No	None
G-05	VASODILATATION	Mild	5	10	Probably	None
	DIARRHEA	Mild			No	None
G-10	ASTHENIA	Moderate	84	1	No	Changed Position
H-03	VASODILATATION	Mild	5	35	Possibly	None
H-31	VASODILATATION	Mild	38	25	Possibly	None
H-34	VASODILATATION	Mild	11	15	Possibly	None
	PARESTHESIA	Mild	11	15	Possibly	None
1-02	RHINITIS	Mild	5	30	No	None
J-01	DIZZINESS	Mild	104		No	Lay Patient Down

Table 3

DISTRIBUTION OF PATIENTS EXPERIENCING ADVERSE EVENTS FOLLOWING INJECTION OF Tc 99m LeuTechTm.		
COSTART	OVERALL'	DRUG-RELATED
	N	N (%)
ANY EVENT (I OR MORE)	17(8)	10(5)
ASTHENIA	1(<1)	0
DIARRHEA	1(<1)	0
DIZZINESS	2(1)	1(<1)
DYSPNEA	3(2)	2(1)
HEADACHE	2(1.0)	1(<1)
INJECTION SITE REACTION	1(<1)	1(<1)
PAIN CHEST	1(<1)	1(<1)
PAIN INJECTION SITE	1(<1)	1(<1)
PARESTHESIA	1(<1)	1(<1)
RHINITIS	1(<1)	0
SYNCOPE	2(1)	0
VASODILATATION	8(4)	8(4)

'Includes drug-related and not drug-related. N is number of patients; % is percentage of patients.

3. Clinical Laboratory Evaluation

Table 4 shows the hematology findings and Table 5 the chemistry findings.

Table 4

SUMMARY OF HEMATOLOGY RESULTS.		
TEST	MEAN AT BASELINE (RANGE) N	MEAN CHANGE AT 2 HOURS (RANGE) N
WBC Count, I 0'/mm'	11.01(0.09-32.71) N = 195	-1.03 (-6.81-6.00) N = 163
RBC Count, 106/mm'	4.65 (2 20-6.45) N = 194	-0.13 (-1.22-0.50) N = 163
Hemoglobin, g/dL	13.67 (6.70-18.80) N= 195	-0.42 (-4 57-2 27) N= 163
Hematocrit, %	40.63 (26.30-54.25) N= 195	-1.13 (-11.57-3.73) N = 163
Platelets, I 0'/mm'	231.67 (59.80-464.38) N = 194	-9.83 (-72 90-66.60) N = 160
Neutrophils, %	72.57 (28.20-99 00) N= 156	-2.12 (-27.00-33.00) N = 129
Lymphocytes, %	20.24 (-11.43-65.71) N= 158	2.59 (-44.0044.29) N = 131
Monocytes, %	9.04 (-3.78-33.78) N= 158	1.21 (-23.11-23.11) N= 130
Eosinophils, %	2.35 (-1.50-14.00) N= 154	-0.10 (-5.00-6.00) N = 128
Basophils, %	0.60 (-3.00-3.00) N= 154	0.15 (-6.00-9.00) N= 128

Table 5

SUMMARY OF CLINICAL CHEMISTRY RESULTS.		
TEST	MEAN AT BASELTNE (RANGE) N	MEAN CHANGE AT 2 HOURS (RANGE) N
AST (SGOT), U/L	15.84 (-2.95-88.44) N = 184	-0.83 (-12.95-10.41) N= 158
ALT (SGPT), U/L	13.49 (-20.57-388.57) N = 177	-1.51(-52.57-5.17) N = 151
Alka. Phos., U/L	170.3 9 (28.00-1475.5 1) N = 184	-6.25 (-152.78-28.40) N= 159
LDH, U/L	176.18 (63.00-352.38) N = 167	-2.33 (-111.46-197.84) N = 142
Total Bilirubin, mg/dL	0.90 (-0.30-3.50) N = 184	0.09 (-0.64-1.40) N= 158
Total Protein, g/dL	7.21 (4.21-8.74) N = 177	-0.29 (-2.70-1.04) N = 150
BUN, (mg/dL)	12.43 (-3.20-81.80) N = 191	-1.26 (-17.00-10.20) N = 167
Creatinine, mg/dL	0.86 (-1.40-22.70) N = I	-0.03 (-0.84-1.60) N = 167

There are numerous laboratory values that reached statistical significance, though most of these were felt to be of clinical significance. Significant changes will be listed below (table 7).

3. Vital Signs

Table 6 shows the vital sign safety data.

Table 6

SUMMARY OF VITAL SIGNS IMMEDIATELY PRIOR TO Tc 99m LeuTechTm INJECTION AND AT THREE POST-INJECTION TIMES.					
SYSTOLIC BP (mm Hg)	N	M-17-7	MAX	MEAN	ST. DEV.
Immediately Pre-Injection	203	90	182	120.0	16.9
Change at 5 Min.	202	-26	42	-0.4	8.2
Change at 30 Min.	201	-22	32	-0.1	8.0
Change at 60 Min.	199	-25	45	0.5	8.2
DIASTOLIC BP (mm Hg)					
Immediately Pre-Injection	203	49	100	72.1	10.6
Change at 5 Min.	202	-24	24	-1.1	6.1
Change at 30 Min.	201	-22	16	-1.2	6.2
Change at 60 Min.	199	-39	14	-1.2	6.1
PULSE RATE (bpm)					
Immediately Pre-Injection	203	50	138	78.8	15.8
Change at 5 Min.	202	-21	30	-0.1	6.5
Change at 30 Min.	201	-20	31	-0.5	6.9
Change at 60 Min.	199	-26	21	-1.7	6.5
ORAL BODY TEMP. (^{0}C)					
Immediately Pre-Injection	202	35.2	40.2	37.1	0.7
Change at 5 Min.	201	-1.3	2.5	0.05	0.4
Change at 30 Min.	200	-1.7	2.7	0.01	0.5
Change at 60 Min.	197	-1.4	2.8	0.02	0.4

C. Individual Clinically Significant Abnormalities

The investigator was to evaluate post-baseline changes in clinical laboratory measurements and to indicate on the CRF the likely cause of any change considered clinically significant, as follows:

1 = Attributable to disease; no follow-up required.
2 = Possibly attributable to Tc 99m LeuTechTm; follow-up required
3 = Apparent laboratory error,
4 = Unevaluable; includes instances where baseline values not reported and instances where sample was hemolyzed.

The four changes in clinical laboratory measurements considered by the investigators to be clinically significant were all attributed to the patients' diseases.

Table 7 represents the clinically significant laboratory changes.

Table 7

INDIVIDUAL CLINICALLY SIGNIFICANT CHANGES IN CLINICAL LABORATORY MEASUREMENT FROM **BASELINE, AT TWO-HOUR POST-INJECTION EVALUATION.**

PT	TEST (normal range)	BASELINE VALUE	NORMAL RANGE	POST-INJECTION VALUE	ATTRIBUTION
D-21	ALT	37.0	6-42	97.0	Disease
	AST	61.0	11-39	154.0	Disease
H-10	Hematocrit	42.8	38-47	32.6	Disease
	Hemoglobin	14.7	12-16	11.2	Disease

Table 8 represents the clinically significant vital sign changes.

Table 8

PT.	Parameter	Baseline value	Post-Injection Value	Post-Injection Time	Attributable to Tc 99m LeuTech
A-13	Diastolic BP	70	31*	I hour	No
A-17	Heart Rate	87	61	1 hour	No
A-18	Heart Rate	60	91	30 min	No
A-27	Heart Rate	65	86	1 hour	No
A-35	Heart Rate	120	95	1 hour	No
B-2	Heart Rate	70	100	5 min.	No
E-22	Systolic BP	147	192	1 hour	No
E-23	Heart Rate	115	94	5 min.	No
H-03	BP	138/74	180/98	5 min.	No

*Diastolic BP was recorded as 31 mm Hg on the source document. Subsequent follow-up BP was 115/70 (time was not specified).

D. Safety Conclusions Phase III Study:

- Tc 991n LeuTechTm appears safe in patients presenting with equivocal signs and symptoms of acute appendicitis.
- No serious or severe adverse events were reported and only three events required action.
- The most frequent adverse event was vasodilatation, reported by 8 patients. It was considered possibly related to the study drug in six patients and probably related in two patients.
- 16 events in 10 patients were considered possibly or probably related to the study drug.
- A number of statistically significant shifts in hematology and clinical chemistry parameters from baseline to post-injection measurement times were recorded; however, they were not considered medically significant.

E. SUMMARY OF ADVERSE EVENTS ALL PATIENTS:

Adverse events from all studies that have used this product are summarized. No new safety concerns are raised by these data.

1. Adverse Events Summarized by Body System:

Table 9 Summarizes Adverse Events by Body Part.

Table 9

Body System	Subjects in All Studies N=393(%)	Subjects in Palatin-sponsored Studies N=277(%)	Patients in Phase *2* and *3* Appendicitis Studies N=259(%)
All Systems	23 (6)	21 (8)	20 (8)
Body As A Whole	8 (2)	6 (2)	5 (2)
Cardiovascular	12 (3)	12 (4)	12 (5)
Digestive	1 (0)	1 (0)	1 (0)
Nervous	3 (1)	3 (1)	3 (1)
Respiratory	5 (1)	5 (2)	5 (2)
Values represent the number (and percent) of subjects with an adverse event in the specified body system.			

2. Adverse Events by Type:

Table 10 Summarizes Adverse Events by Type.

Table 10

Adverse Event Type	No. **of Incidents**	Incidence
Vasodilatation	10	3
Dyspnea	4	1
Headache	2	<1
Pain at Injection Site	2	<1
Syncope	2	<1
Dizziness	2	<1
Asthenia	1	<1
Injection Site Reaction	1	<1
Pain	1	<1
Abdominal Pain	1	<1
Chest Pain	1	<1
Diarrhea	1	<1
Paresthesia	1	<1
Rhinitis	1	<1
Total	30	
Values represent the number and percent of reports of the specified adverse events in 393 total subjects in all studies.		

F. Summary

As noted by all the safety data presented, no major safety concerns were identified in either the phase II or phase III trials. The data representing HAMA evaluation and validation is still undergoing review. This product will be indicated for single use only until further safety data and assay validations are conducted to ensure the safety of repeat administration.

Appendix A – "Other Infections"

A. Introduction

LeuTech has been studied for the indication of diagnosing atypical appendicitis. Additional information from the phase II and phase III studies was gathered in regards to other abdominal infections. These data are presented below.

B. Phase II

1. Blinded Readers: Infection

Efficacy outcomes were calculated for abdominal infections other than appendicitis. Scans were read as positive or negative for infection. If positive for infection, the scan was then read as positive for appendicitis (uptake in the appendicitis zone), or positive for another infection. This is a secondary outcome measure for this study. The efficacy outcome measures are similar to those for appendicitis. Sensitivity is better than specificity. Table 10 shows the blinded reads.

Table 1

BLINDED READER: Tc 99m LeuTechTm IMAGES, INFECTION/NO INFECTION.					
EVALUATION	NT	TP + TN	Agreement Rate %	95% Confidence Int.	
				LL	UL
READER1	56	44	79	65.2	87.5
READER2	56	47	84	71.2	91.4
READER3	56	44	79	65.2	87.5
AGGREGATE	56	45	**80**	67.2	88.8
EVALUATION	N(+)	TP	Sensitivity	95% Confidence Int.	
				LL	UL
READERI	35	31	89	72.3	95.0
READER2	35	29	83	65.7	91.7
READER3	35	29	83	65.7	91.7
AGGREGATE	35	30	**86**	69.0	93.4
EVALUATION	N(-)	TN	Specificity	95% Confidence Int	
				LL	UL
READER1	21	13	62	38.7	79.4
READER2	21	18	86	62.6	93.9
READER3	21	15	71	47.7	86.0
AGGREGATE	21	15	**71**	47.7	86.0
EVALUATION	TP+FP	TP	PPV	95% Confidence Int.	
				LL	UL
READER1	39	31	80	63.1	89.2
READER2	32	29	91	73.8	95.9
READER3	35	29	83	65.7	91.7
AGGREGATE	36	30	**83**	66.5	92.0
EVALUATION	TN+FN	TN	NPV	95% Confidence Int.	
				LL	UL
READER1	17	13	77	49.8	89.6
READER2	24	18	75	52.9	87.8
READER3	21	15	71	47.7	86.0
AGGREGATE	20	15	**75**	50.6	88.4

2. On-Site Readers: Infection

Table 12 shows the efficacy outcome measures for on-site readers. The efficacy outcome measures for infection with onsite readers mirror the findings for appendicitis.

Table 2

SITE INVESTIGATORS: PATIENT-BASED AGREEMENT RATE, SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE AND NEGATIVE PREDICTIVE VALUE OF Tc 99m LeuTechTm IMGES WITH FINAL INSTITUTIONAL DIAGNOSIS, INFECTION/NO INFECTION.

AGREEMENT RATE	N (T)	TP + TN	Agreement Rate (%)	95% Confidence Int. LL	UL
SITE A	49	45	92	79.5	96.4
SITE B	7	5	71	30.3	88.3
Combined	56	50	**89**	77.4	94.9
SENSITIVITY	N(+)	TP	Sensitivity	95% Confidence Int. LL	
SITE A	29	29	100	85.4	100
SITE B	6	4	7	24.1	86.8
Combined	35	33	**94**	79.5	97.2
SPECIFICITY	N(-)	TN	Specificity	95% Confidence Int. LL	UL
SITE A	20	16	80	55.7	91.2
SITE B	I	1	100	5.5	100
Combined	21	17	**81**	57.4	91.6
POSITIVE PREDICTIVE VALUE	TP + FP	TP	Positive Predictive Value	95% Confidence Int. LL	UL
SITE A	33	29	88	70.9	94.7
SITE B	4	4	100	39.6	100
Combined	37	33	**89**	73.6	95.2
NEGATIVE PREDICTIVE VALUE	TN + FN	TN	Negative Predictive Value	95% Confidence Int. LL	UL
SITE A	16	16	100	75.9	100
SITE B	3	1	33	1.8	76.8
Combined	19	17	**90**	65.5	95.

N (T) is total number of patients with a final institutional diagnosis.
N (+) is total number of patients with a final institutional diagnosis of "infection".
N (-) is total number of patients with a final institutional diagnosis of "no infection".

B. Phase III

The phase III study was designed address the utility of LeuTech in the diagnosis of atypical appendicitis. When scans were read, they were categorized as infection/no infection. This was further broken down to appendicitis/other infection. Presented below is information regarding the diagnosis of infection/no infection, in addition to characterizing the other types of infection that were observed.

Twenty-three (23) patients whose final institutional diagnosis was negative for appendicitis were positive for "other infection". Three patients were diagnosed with both acute appendicitis and another infection. The total number of patients who were positive, N (+), changed from 59 for appendicitis to 82 for infection and the total who were negative, N (-), from 141 for appendicitis to 118 for infection. Aggregate sensitivity for infection/no infection (73%) was slightly lower than aggregate sensitivity for appendicitis/no appendicitis (75%), whereas aggregate specificity was higher for infection/no infection (99%) than for appendicitis/ no appendicitis (93%). Accuracy of blinded readers' evaluations for infection/no infection was comparable to accuracy for appendicitis/no appendicitis. PPV was better for infection/no infection (aggregate = 98%) than for appendicitis/no appendicitis (aggregate = 82%). In contrast, NPV was better for appendicitis/no appendicitis (aggregate = 90%) than for infection/no infection (aggregate = 84%).

1. Distribution of infections other than acute

Table 1 shows the distribution of other infections.

Table 3

FINAL DIAGNOSIS	N (%)
Diverticulitis	4 (2%)
Colitis and/or Enteritis	4 (2%)
Periappendicitis[1]	3 (2%)
Peritonitis[2]	3 (2%)
Gastroenteritis	2 (I.0%)
Urinary Tract Infection	2 (I.0%)
Intraperitoneal Bladder Rupture	1 (<1%)
Pelvic Infection	1 (<1%)
Retrocecal Abscess	1 (<1%)
Terminal Ileal Crohn's Disease	1 (<1%)
Hidradenitis abscess	1 (<1%)
Pyelonephritis	1 (<1%)
Perforated Gangrenous Gall Bladder	1 (<1%)
Colonic Mass	1 (<1%)

[1]One patient (B- 10) was diagnosed with acute appendicitis and periappendicitis.
[2]Two patients (D-22, G-05) were diagnosed with acute appendicitis and peritonitis.

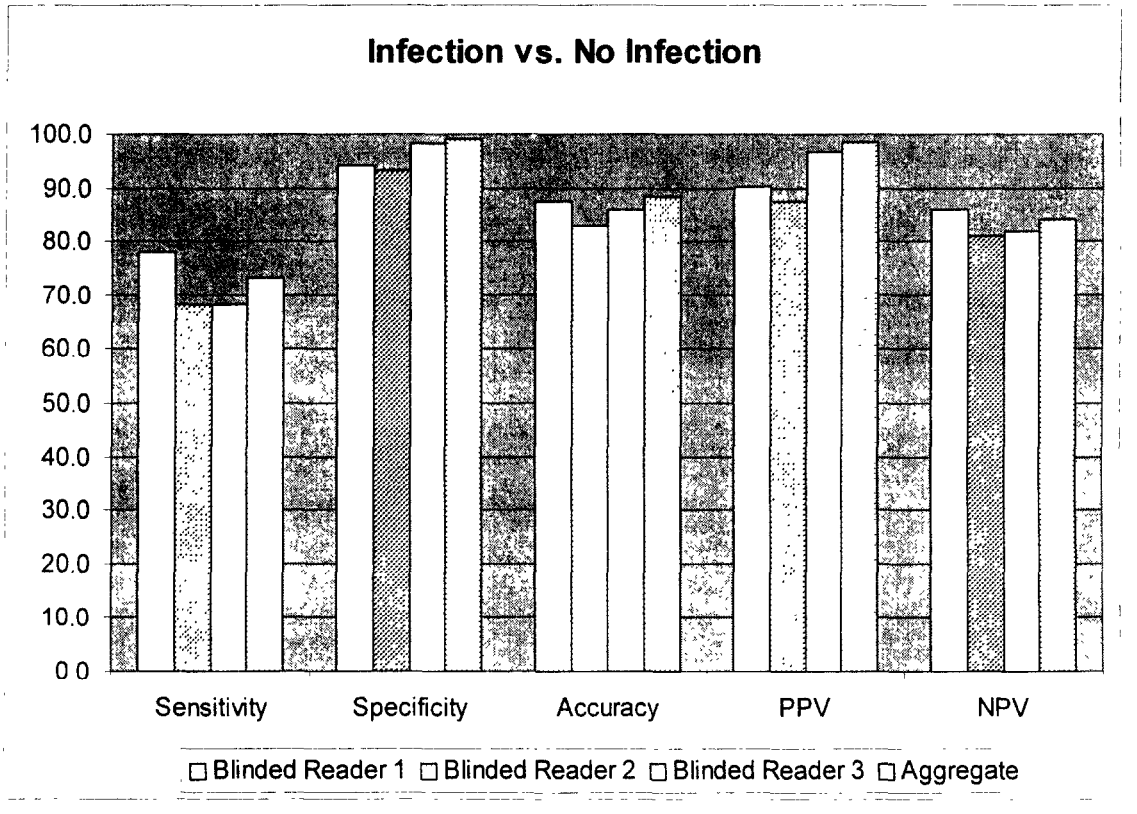
2. Blinded Readers – Efficacy

BLINDED READER: SENSITIVITY, SPECIFICITY, ACCURACY, PPV AND NPV Tc 99m LeuTechTm IMAGES OF EVALUABLE PATIENTS (200) INFECTION / NO INFECTION

Table 4 **(sponsor)**

EVALUATION	Sensitivity	Specificity	Accuracy	PPV	NPV
Blinded Reader 1	78	94	88	90	86
Blinded Reader 2	68	93	83	88	81
Blinded Reader 3	68	98	86	97	82
Aggregate	73	99	89	98	84

Chart 1



4. Likelihood Ratios

LIKELIHOOD RATIOS OF BLINDED READERS'EVALUATIONS OF Tc 991n LeuTechTm IMAGES FOR INFECTION/NO INFECTION, EVALUABLE PATIENTS.

Table 5

EVALUATION	LR(+)	95% Confidence Interval	LR(-)	95% Confidence Interval
Blinded Reader 1	13.2	6.36-27.24	0.2	0.16-0.35
Blinded Reader 2	10.1	5.08-19.99	0.3	0.25-0.47
Blinded Reader 3	40.3	10.12- 160.48	0.3	0.24-0.44
Aggregate	86.3	12.21- 610.54	0.3	0.19-0.39

Blinded readers' positive test interpretations increased the odds that a patient had an infection by 10- to 40-fold, compared to pre-Tc 99m LeuTech odds. Given the aggregate blind read results, a positive Tc 99m LeuTech study increased the odds that a patient had an infection by a multiple of 86, compared to their pre-test odds. Blinded readers' negative test interpretations decreased the odds that a patient had an infection by a factor of 1/5 to 1/3, compared to pre-Tc 99m LeuTech odds. Given the aggregate blind read results, a negative Tc 99m LeuTech study decreased the odds that a patient had an infection by a factor of approximately 1/4. Considering the likelihood ratios for infection/no infection compared to the likelihood ratios for appendicitis/no appendicitis, LR (+) for the aggregate blinded read was much higher for infection than for appendicitis, 86.3 versus 10.5, respectively. LR (-) for appendicitis and infection for the aggregate blinded read were the same, 0.27.

C. Pooled Data Phase II and Phase III

The specificity for an infectious etiology approached 100% for the blinded reader aggregate, though it was only 84%for the onsite readers. The sensitivity for the onsite readers was over 90% with a 78% rate for the blinded readers.
The likelihood ratios are shown in table 7.

1. Efficacy

Table 6 shows the sensitivity, specificity, accuracy, PPV and NPV of blinded readers' evaluations of Tc 99m LeuTechTm images for infection/no infection, evaluable patients, studies 98-004 and 97-003

Table 6

SENSITIVITY				
EVALUATION	N(+)	TP	**Sensitivity**	95% Lower Limit
Blind-Read Aggregate'	117	90	78	70.9
Site Investigators	111	102	92	86.0
SPECIFICITY				
EVALUATION	N(-)	TN	**Specificity**	95% Lower Limit
Blind-Read Aggregate	139	132	99	95.8
Site Investigators	127	106	84	76.9
ACCURACY				
EVALUATION	NT	TP	**Accuracy**	95% Lower Limit
Blind-Read Aggregate	256	222	87	83.2
Site Investigators	238	208	87	83.2
PPV				
EVALUATION	TP+FP	T?	PPV	95% Lower Limit
Blind-Read Aggregate	97	90	97	92.5
Site Investigators	123	102	83	76.2
NPV				
EVALUATION	TN + FN	TN	NPV	95% Lower Limit
Blind-Read Aggregate	159	132	83	77.6
Site Investigators	115	106	92	86.5

N(+) is the number of patients positive for infection by final institutional diagnosis.
N(-) is the number of patients negative for infection by final institutional diagnosis.
N T is the total number of patients.
'Blind-read aggregate estimates based on weighted 98-004 and 97-003 estimates.

2. Likelihood Ratios: Other Infections

Likelihood Ratios of Tc 99m LeuTechTm Images for Infection/No Infection, Evaluable Patients Studies 98-004 and 97-003'

Table 7

EVALUATION	LR(+)	95% C. 1.	LR(-)	95% C. 1.
Blind-Read Aggregate	4.35	2.27-8.34	0.26	0.19-0.36
Site Investigators	5.56	3.75-8.25	0.10	0.05-0.18
'Estimates based on weighted 98-004 and 97-003 estimates.				

The likelihood ratios as calculated from the data for infection are similar to those calculated for appendicitis.

C. Summary:

Though LeuTech demonstrated similar sensitivity and improved specificity at identifying infections vs. no infections, this study was not designed to determine the utility of this information. The ability to identify what type of infection, and the small number of patients with infections other than appendicitis contribute to the lack of significance of these data as related to the primary goal of the development of this product for use in patients with atypical appendicitis.
Further studies would be required to delineate the role of LeuTech in the diagnosis of patients with abdominal pain and any type of infectious etiology.

Appendix B – CT Scan

A. LeuTech and CT Scans

Within in the phase III study, 49 patients underwent CT scanning in addition to having had their LeuTech scan. The table below depicts the outcomes of LeuTech and CT scans as they relate to the final diagnosis. This table does not differentiate spiral from conventional CT scans. Additionally the interpretation of the CT scans was not prospectively defined to be either positive or negative with no middle ground. Despite these issues, LeuTech performed quite similarly to CT scanning in these 49 patients.

1. Comparison of LeuTech and CT results, (N=49)

Table 1

	CT				
Tc 99m LeuTechTm	TP	FN	TN	FP	Totals
TP	7	3			10
FN	I	I			2
TN			29	3	32
FP			4	1	5
Totals	8	4	33	4	**49**

2. Efficacy of LeuTech vs. CT Scan

Table 2

N=49	LeuTech	CT Scan
Sensitivity	83	67
Specificity	86	89
Accuracy	88	84
PPV	67	67
NPV	94	89

Efficacy parameters were calculated on this small subset of patients. The tests performed similarly, though LeuTech had a greater sensitivity. This trial was not designed to study and compare these two modalities.

3. Distribution of Planned diagnostic procedures relative to LeuTech scanning

Surgeons were asked both prior to and after the LeuTech scan what further diagnostic testing would they perform. These data are depicted below.

Table 3

	PATIENTS	
PRIOR TO Tc 99m LeuTechTm	N	%
Conventional CT	28	15
Spiral CT	17	9
Ultrasound	17	9
Barium Enema	2	1
Other	9	5
AFTER Tc 99m LeuTechTm		
Conventional CT	25	13
Spiral CT	12	6
Ultrasound	7	4
Barium Enema	3	2
Other	6	3

Percentages are calculated for N=189. (10 patients had pre and post scan forms filled out by different surgeons, 1 patient was excluded because the pre-scan form was filled out after the study).