CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852
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To: STN # 103928/0

Topic: Clinical Review

STN # 103928/0
Product: NeutroSpec®, Technetium Tc 99m Fanolesomab
Indication: Diagnosis of Appendicitis
Sponsor: Palatin

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

The data reviewed in this BLA (103928/0,Palatin, Technetium Tc 99m Fanolesomab) support the approval of the new drug to diagnose appendicitis in patients presenting with atypical signs and symptoms. This recommendation is based on a review of Technetium Tc 99m fanolesomab activity, safety, pharmacokinetic, and dosing information in adult and pediatric patients above 5 years of age.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The mechanism of the drug product is related to accumulation of polymorphonuclear leukocytes (PMNs) to the inflamed appendix. Patients who may have extremely low high PMNs counts may have different response to the administration of Technetium Tc 99m fanolesomab.In addition the presence of HAMA in patients may interfere with murine antibody based immunoassays, compromise the efficacy of diagnostic or therapeutic murine antibody-based agents, and increase the risk of adverse reactions.

Therefore it is recommended to further study of Technetium Tc 99m fanolesomab in patients who have equivocal signs and symptoms of appendicitis and low PMNs and to obtain data on clinical significance of the HAMA by using a validated assay that would be essential to fully understand the product activity and safety. The sponsor should provide these data after the approval of Technetium Tc 99m fanolesomab.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The applicant submitted a Biologics License Application for Technetium Tc 99m fanolesomab kit for the preparation of Technetium Tc 99m fanolesomab for the diagnosis of appendicitis in patients with equivocal signs and symptoms.

Prior to the submission of the BLA the applicant had a pre-BLA meeting on May 20, 1999. In December 06, 1999, the applicant submitted a BLA with efficacy and safety data (study 97-003, 98-004) and additional safety data from a total of 14 other trials.

Technetium Tc 99m fanolesomab was evaluated for imaging efficacy and safety in two clinical trials in patients with equivocal signs and symptoms of appendicitis. Both the phase two (97-003), and phase three trials (98-004) were conducted under similar protocols. Both protocols sought to enroll patients with atypical signs and symptoms of

appendicitis. The agreement between the blinded reader's diagnosis and the diagnosis from the institution (pathological) determined efficacy endpoints in similar fashion in both studies.

A total of 259 patients were studied in the phase 2 and phase 3 appendicitis trials. The incidence of appendicitis in the phase 2 and phase 3 study was 50% and 30% respectively.

The results of the above studies were reviewed by the agency and presented to a Medical Imaging Device Advisory Committee (MIDAC) on July 10, 2000. At that time, the MIDAC unanimously voted in favor of the adequacy of the data to support the safety and efficacy of the scan using Technetium Tc 99m fanolesomab.

This review summarizes the previous evaluation of the original BLA by the clinical reviewer (Dr Robert Lindblad) in addition to the review of new safety data from additional 84 patients that was provided in a follow-up submission on 11 February 2004, by Palatin, Inc. The overall safety data was obtained from 523 patients of which 259 were enrolled in the phase 2 and phase 3 appendicitis trials.

B. Efficacy

Efficacy was evaluated in 259 patients who participated in studies 97-003 (phase 2) and 98-004 (phase 3) for appendicitis. Both studies were designed to assess the efficacy of Tc 99m Technetium Tc 99m fanolesomab imaging for detection of acute appendicitis.

The performance of Technetium Tc 99m fanolesomab was based on the readings of the Technetium Tc 99m fanolesomab imaging by three experienced blinded nuclear medicine practitioners and the by the site investigators for the presence or absence of infection and, specifically, as "appendicitis" or "no appendicitis". The primary performance outcome was the rate of agreement between the diagnosis made by the blinded readers and the institutional final clinical diagnosis. For cases that underwent surgery, the surgical and pathology reports were the basis for the final diagnosis. In the event surgery was not performed, clinical follow up was obtained with in 2 weeks for the phase 3 and with in 4 weeks for the phase 2 study. Secondary performance outcome measures included patient-based rates of agreement of the individual site investigators assessments of the Tc 99m Technetium Tc 99m fanolesomab scans for the presence or absence of appendicitis compared with final institutional diagnosis. Associated measures of sensitivity, specificity, negative and positive predictive value for blinded readers, site investigators and impact on clinical management as assessed by the comparison of the pre- and post-Technetium Tc 99m fanolesomab imaging questionnaires were obtained.

The primary efficacy analysis evaluated the performance of Technetium Tc 99m fanolesomab for diagnosis of acute appendicitis in both studies. The two clinical trials used the agreement rate as the primary efficacy outcome measure. 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 intent to treat (ITT) analysis.

The performance rates for the diagnosis of appendicitis by the blinded readers and by the clinical investigators for study 98-004 are shown in Table 1.

Table 1. Phase 3 Diagnostic Performance Of Technetium Tc 99m Fanolesomab

Evaluation	Performance Rates	
	Blinded Readers percentages (95%CI)	**Study Investigators** percentages (95%CI)
Sensitivity	75 (62, 85)	91 (80, 97)
Specificity	93 (87, 97)	86 (79, 91)
Accuracy	87 (82, 92)	87 (81, 91)
Positive Predictive Value	82 (69, 91)	74 (62, 84)
Negative Predictive Value	90 (84, 94)	96 (90, 99)

For blinded readers scintigraphy with technetium Tc 99m fanolesomab had a sensitivity of 75%, a specificity of 93% and an accuracy of 87% for a diagnosis of appendicitis. The positive predictive value and negative predictive value were 82% and 90%, respectively. For investigators at the clinical sites (site investigators), scintigraphy with technetium Tc 99m fanolesomab had a sensitivity of 91%, a specificity of 86% and accuracy of 87%. For the site investigators, the positive predictive value and negative predictive value were 74% and 96%, respectively. Analyses by various demographic characteristics suggested that the performance of technetium in these subgroups was similar to that of the overall study population.

The above study results are supported by similar findings from the phase 2 trial that was conducted in 56 patients with equivocal signs and symptoms of appendicitis. The phase 2 study demonstrated that technetium Tc 99m fanolesomab had 89% sensitivity, 68% specificity, 73% PPV and 86% NPV as per the blinded reader assessments.

C. Safety

The safety information was obtained from 523 patients who received technetium Tc 99m fanolesomab in 14 trials. Four hundred seven (407) patients were enrolled in eleven studies sponsored by Palatin Technologies, Inc. Of the 523 patients 259 participated in the phase 2 and phase 3 studies for appendicitis.

Patients ranged in age from 5.2 years to 91 years, with the median age of 35 years. Twenty-nine (5.5%) patients were between 5 and 11 years of age and 32 (6.1 %) were between 12 and 16 years. Sixty-four patients (12.2%) were 65 years of age or older. Two hundred seventy nine (53%) were female and 244 (47%) were male. There were

319 (61%) whites, 49 (9%) blacks, 98 (19 %) Hispanics, and 33 (6%) "other". For studies under Palatin INDs and for the appendicitis studies, the proportions of Caucasians patients were higher, 72% and 66%, respectively than other racial groups.

All patients received a single injection of Tc 99m Technetium Tc 99m fanolesomab, except for the 30 patients enrolled in Study 99-001, who received two injections of radioactively decayed Technetium Tc 99m fanolesomab to evaluate HAMA response. A total of 30 patients enrolled in Study 97-001 received a single injection of decayed Technetium Tc 99m fanolesomab to evaluate HAMA response.

The average antibody dose was 121 ug (range 32.5 ug to 250 ug). Excluding the patients who received decayed Technetium Tc 99m fanolesomab in studies 97-001 and 99-001, the radioactive dose ranged from 1.1 mCi to 33.0 mCi, with a mean of 15 mCi.

Thirty-seven of the 523 patients (7%) who received technetium Tc 99m fanolesomab reported a total of 49 adverse events (AEs). Of the 49 AEs reported, 4 (8%) were classified as severe: (pain, decrease in O2 saturation (68%) with chest pressure, sepsis and hypotension). Two of the 4 severe adverse events were serious adverse events and were accompanied by death. The four patients with severe adverse events are described below:

1) A 66-year-old man with diabetes mellitus and end stage renal disease, peritoneal dialysis catheter infection developed severe hypotension 7 hours after technetium Tc 99m fanolesomab injection and suffered cardiac and respiratory arrest. The cause of death was uncertain. The AE s were considered unrelated to the study drug by the investigators.

2) A 35 years old woman with diabetes mellitus, decubitus ulcer, sepsis, and respiratory failure received technetium Tc 99m fanolesomab injection for assessment of infection, continued to deteriorate and died 8 days later.

3) The third patient had a non-specified pain for 3 hours that started immediately after technetium Tc 99m fanolesomab injection.

4) An adult patient experienced chest pressure and decreased oxygen saturation 5 minutes post injection. The symptoms persisted for about 48 minutes. The patient required oxygen therapy and later recovered. These AE s were considered as possibly related to the study drug by the investigator. The adverse events in this patient were initially classified as moderate by the investigator.

Thirty-five (71%) AEs were classified as mild in severity and 10 (20%) were moderate.

A total of 24 of the 49 AEs were considered possibly or probably related to the study drug and were experienced by sixteen (3%) of 523 patients. The events included 10 cases of flushing, 3 cases of dyspnea, 2 cases of chest pressure sensation, and single

cases of nausea, injection site burning, injection site erythema, pO2 decrease, dizziness, headache, paresthesia, contusion and hot flushes.

The most frequently reported AE was flushing, experienced by 10 patients (1.9%). Dyspnea was reported by 5 (1.0%) patients. Dizziness and paresthesia were reported in 3 patients (0.6%) each. Nausea, chest pressure, pain, nasopharyngitis, headache, hypotension and syncope were reported in 2 patients (0.4%) each. Action was taken for 5 AE s (dizziness; weakness; syncope; chest pressure and decrease in pO2; each involved a change in body position (place to supine position) to resolve the event. All AEs had resolved by the end of the study period.

Time of onset ranged from immediately post-injection to 4.5 days post- injection and duration ranged from 1 minute to 4 hours in cases where onset and duration were specified (excluding LT-006-02, subject 1012 who had a pre-existing condition of sepsis).

For 441 patients, changes in vital signs were evaluated at 5 minutes, 30 minutes and 1-hour post injection. Statistically significant decreases in systolic and diastolic blood pressures were noted following injection, and a statistically significant decrease in pulse rate was noted at 1-hour post-injection. However, the changes were small and not clinically significant.

Clinical laboratory parameters were measured and evaluated for changes from baseline in four studies. A total of 7 clinically significant changes in laboratory parameters were reported in 4 of the 284 patients (1.4%). The only clinically significant changes in laboratory parameters that were possibly attributed to technetium Tc 99m fanolesomab were elevations in AST and LDH in one subject after a second injection. These elevated liver enzymes returned to baseline without treatment; clinical and laboratory follow-up revealed no cause, so the investigator was unable to exclude the possibility of relationship to the injection of technetium Tc 99m fanolesomab.

For the phase 3 appendicitis study and the phase 2 osteomyelitis study, statistically significant shifts downward in laboratory parameters were noted at 2 hours post-injection for WBC, neutrophils, hemoglobin, total protein and BUN.

Twenty of 39 shifts were a transient decrease in Hct and 15 of the 24 shifts were a reduction in RBCs. Downward shifts in neutrophil counts have been observed in 28 (18.5%) of 151 patients. Twenty-six of 188 (13.8%) patients demonstrated a negative shift in WBCs at 2 hours post injection. There was a tendency to shift upward for relative differential count for lymphocytes (19 of 29 shifts) and for monocytes (17 of 22 shifts). Two patients were observed to develop elevations of AST and ALT after Technetium Tc 99m Fanolesomab administration. These changes were judged to be of no clinical importance.

WBC and granulocyte counts demonstrated partial recovery by 4 hours post injection. There was no evidence of adverse reactions to the shifts in neutrophils. The shifts in the other laboratory parameters (hemoglobin, total protein AST, ALT BUN) were not believed to be related to study drug.

None of the 54 patients having HAMA assays before and after a single injection of technetium Tc 99m fanolesomab had a positive HAMA response at any time point. Five (16.7%) of the 30 patients who received two injections of technetium Tc 99m fanolesomab exhibited positive HAMA responses.

In summary, technetium Tc 99m fanolesomab has an acceptable safety profile in all studied populations, including the pediatric, adult and geriatric populations, for use according to the proposed indication. Further studies will be needed to demonstrate activity and safety in a neutropenic population.

D. Dosing

The average antibody dose used for all 523 patients was 121 ug (range 32.5 ug to 250 ug). Excluding the patients who received decayed Technetium Tc 99m fanolesomab in studies 97-001 and 99-001, the radioactive dose ranged from 1.1 mCi to 33.0 mCi, with a mean of 15 mCi.

In the appendicitis studies adult patients received a single IV injection of Technetium Tc 99m fanolesomab injection administered in a single dose with 10 to 20 mCi (370 to 740 MBq) of technetium-99m, corresponding to 75 to 125 µg of fanolesomab. The dose for pediatric patients (5-17 years of age) was 0.21 mCi per kilogram of body weight, up to a maximal dose of 20 mCi.

E. Special Populations

Use in Pregnancy

Animal reproduction studies have not been conducted with technetium Tc 99m fanolesomab. It is also not known whether technetium Tc 99m fanolesomab can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Therefore Technetium Tc 99m fanolesomab is classified, as Pregnancy Category C.

Nursing Mothers

The product was not studied in nursing mothers. It is not known whether this drug is excreted in human milk.

Pediatric Use

Technetium Tc 99m fanolesomab was studied in a total of 61 pediatric patients. A total of 29 (5%) were 5–11 years old and 32 (6%) were 12–16 years old. No overall differences in safety or effectiveness were observed between these patients and patients in other age brackets.

Medical Reviewer Comment: *The number of pediatric subjects in the study was small. Though the data did not demonstrate a difference in safety and effectiveness compared to adults, a meaningful overall conclusion cannot be made.*

Geriatric Use

In clinical studies of Technetium Tc 99m fanolesomab, 64 (12%) patients were 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Medical Reviewer Comment: *The number of geriatric subjects in the study was small. Though the data did not demonstrate a difference in safety and effectiveness compared to younger patients, a meaningful overall conclusion cannot be made.*

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Sponsor:	Palatin Technology
Drug Product:	Generic: Sodium Pertechnetate Tc 99m labeled Murine Monoclonal Antibody
Trade Name:	NeutroSpec
Dosage Forms:	Sodium Pertechnetate Tc 99m: 10 to 20 mCi (370 to 740 MBq)
	Murine Monoclonal Antibody: 75-125ug/ single dose
Routes of Administration:	IV
Indication Studied:	Diagnosis of Equivocal Appendicitis
Age Groups:	5 years and above

B. State of Armamentarium for Indication(s)

Although the diagnosis of appendicitis is usually straightforward, there are cases with equivocal symptoms and signs where further testing beyond the history and physical exam is required. If the diagnosis is still in question, radiological evaluation is usually pursued. Anatomical imaging such as abdominal CT scans have been a useful aid in making the diagnosis of appendicitis and also identifying other etiologies for the presenting symptoms.

Technetium Tc 99m fanolesomab provides an additional and different approach in diagnosis of appendicitis. The murine monoclonal IgM antibody (fanolesomab) recognizes CD15 antigens that are expressed on human polymorphonuclear neutrophils (PMNs). The radiolabeled antibody binds in vivo to PMNs that localize in the inflamed appendix. By nuclear medicine imaging of radiolabeled WBC (physiologic function), sites of inflammation, specifically the appendix, could potentially be identified.

C. Important Milestones in Product Development

The applicant submitted a Biologics License Application for Technetium Tc 99m fanolesomab® Kit for the preparation of Technetium Tc 99m fanolesomab®, seeking the indication of the diagnosis of appendicitis in patients with equivocal signs and symptoms.

In December 06, 1999, the applicant submitted a BLA (99-1407) in which Tc 99m Technetium Tc 99m fanolesomab® was evaluated for imaging efficacy and safety in two clinical trials (98-004 and 97-003), one of which was a Phase 3 (98-004), to diagnose appendicitis in patients with equivocal signs and symptoms. The study protocol and the imaging techniques were the same in both studies except for minor differences. A total of 259 patients were studied in both trials.

The results of the above studies were reviewed by the agency and a Medical Imaging Device Advisory Committee (MIDAC) on July 10, 2000. . The results of the above studies were initially reviewed by the agency (Robert Lindblad, MD) and presented to a Medical Imaging Device Advisory Committee (MIDAC) on July 10, 2000. At that time, the MIDAC unanimously voted in favor of the adequacy of the data to support the safety and efficacy of the scan using Technetium Tc 99m fanolesomab. Because of issues related to manufacturing the product, the drug was not approved for marketing at that time

This review re-examines the previous evaluation of this BLA by Dr Robert Lindblad in addition to the review of the new safety data from additional 84 patients that has been provided since the submission of the 120-Day Safety Update on 28 March 2000.The updated Integrated Safety Summary (ISS) in a follow-up submission was submitted 11 February 2004, by Palatin, Inc and contains a safety data from additional 84 patients exposed to the Technetium Tc 99m fanolesomab. The overall safety data was obtained from 523 patients.

D. Other Relevant Information

None.

E. Important Issues with Pharmacologically Related Agents

There are no known labeling changes, safety or effectiveness concerns with other related agents.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Please see reviews by product and toxicology reviewers for details

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Please see the pharmacologist's review for details

In a study of 10 healthy volunteers, following intravenous injection of technetium Tc 99m fanolesomab, blood concentrations of radioactivity decreased rapidly with an initial half-life of 0.3 hours and a second phase half-life of about eight hours. Whole-body scintigraphy at two hours post-injection indicated that the liver had the highest radioactivity uptake and retention (50% of the injected dose), followed by the kidney, spleen and red marrow. Over 26–33 hours after injection, 38% of the injected dose of radioactivity was recovered in urine.

The metabolic profile of fanolesomab has not been established. Specific studies on drug interaction with technetium Tc 99m fanolesomab have not been conducted.

B. Pharmacodynamics

Please see the pharmacologist's review for details

IV. Description of Clinical Data and Sources

A. Overall Data

The material reviewed in this BLA 103928/0 (Palatin, Technetium Tc 99m Fanolesomab) was derived from two clinical trials (97-004 and 97-003), one of which was a Phase 3 (97-004), that were conducted to diagnose appendicitis in patients with equivocal signs and symptoms. A total of 259 patients were studied in both trials. The safety material reviewed in this BLA was derived from clinical studies conducted by the applicant and other investigators from a total of 14 studies where Technetium Tc 99m Fanolesomab was used. The sponsor provided safety data on an additional 84 patients in this re-submission response to the CR letter.

B. Tables Listing the Clinical Trials

The summary of the applicant's two studies for the above indication and other conditions is presented in Table 2. The total number of patients studied is 523.

Table 2 Clinical Studies

	Design	Antibody Doses	Patients
Phase II (Study 97-003)	Open label within-patient comparative Patients with suspected appendicitis	87.5ug-143.7ug	56 patients, two sites, 8 years of age and older
Phase III (Study 98-004)	Open label within-patient comparative Patients with suspected appendicitis	32.5-250 ug	203 patients, multicenter, ten sites, 5 years of age or older.
Phase I (Study 97-002)	Open label to evaluate biodistribution, safety, radiation dosimetry, in normal volunteers	67.5-127.5 ug	10 patients
Phase II (98-005)	Diagnosis of Osteomyelitis	125 ug	24 patients
Phase I (97-001)	Open label, HAMA response following 2 injections of non radioactive Technetium Tc 99m fanolesomab	125ug	30 healthy volunteers
Phase I (99-001)	Open label, HAMA response following injections of non radioactive Technetium Tc 99m fanolesomab in healthy volunteers	125ug	30 healthy volunteers
Phase I/II (95-001)	Open label, within patient comparative. Infectious and inflammatory Process	62.5-200.9ug	69 patients
Phase I (Gratz-Becker)	Open label, within patient comparative. Infectious Process	100 ug	17 patients
Phase I (99-005)	Open label, to evaluate drug biodistribution. Pediatric patients with suspected appendicitis	75-87.5 ug	2 patients
Phase II (99-003)	Open label, within patient comparative. Prosthetic joint infection	125-200 ug	22 patients
Phase II (99-004)	Open label, within patient comparative. Diabetic foot ulcers	125 ug	26 patients
Phase II (99-006)	Open label, within patient comparative. Post surgical abscess	125 ug	8 patients
Phase II (LT-006-02)	Open label, within patient comparative. Suspected occult infection	100-125 ug	19 patients
Phase II (LT-007-02)	Open label, within patient comparative. Post surgical infection	125 ug	7 patients

C. Post marketing Experience

The product is not approved in any country.

D. Literature Review

The reprints of articles on Tc 99m Fanolesomab and its effect on PMN function was submitted by the sponsor and reviewed. These reviewed articles include:

1. Monoclonal antibodies as agents for selective radiolabeling of human neutrophils, ML Thakur, MD Richard and FW White 3d,;Journal of Nuclear Medicine, Vol 29, Issue 11 1817-1825,

2. Intraindividual comparison of 99mTc-labelled anti-SSEA-1 anti-granulocyte antibody and 99mTc-HMPAO labelled white blood cells for the imaging of infection. Gratz S, Behr T, Herrmann A, Dresing K, Tarditi L, Franceschini R, Rhodes B, Stürmer KM, Becker W.; Eur. J. Nucl. Med. 25, 1998; 386-393,

V. Clinical Review Methods

Dr Lindblad, a medical reviewer in the Office of Therapeutics Research and Reviewer in CBER performed the clinical review of the original submission STN 103928 (see Dr Lindblad's review). Dr Lydia Martynec, or nuclear medicine reviewer preformed a review of the review of radiation dosimetry with particular emphasis on image acquisition and interpretation (see Dr Martynec's review). FDA presented the findings to the medical Imaging Drugs Advisory Committee on July 10, 2000.

The clinical review of STN 103928/0 (Palatin, Technetium Tc 99m Fanolesomab) recapitulated the findings by Dr Lindbald and updated the safety data to the original submission. The review of the additional safety data was done using study reports, summary tables and line listings.

A. How the Review was Conducted

The review of the updated safety data was conducted using clinical study reports and summary tables and line listings.

Safety was assessed by integrating the data of the applicant-sponsored trials and other studies, where the product was used.

Study reports, line listings, and Case Report Forms were reviewed. The safety review also consisted of a review of all adverse events including laboratory abnormalities by summary tables and line listings, along with review of physical examination line listings.

B. Overview of Materials Consulted in Review

Updated safety reports, the clinical review by Dr Lindblad and transcripts of the July, 2000 MIDAC meeting were used for the review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Two clinical investigator sites were inspected by DSI. The inspection demonstrated that there was sufficient documentation to assure that all study subjects consented properly, study eligibility criteria were fulfilled, participants received assigned study drug, and adverse events were adequately reported.

There were no reported discrepancies in the management and reporting of data.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

There was no evidence to suggest that the studies contained in this BLA were not conducted in accordance with accepted ethical standards and under good clinical practices. Valid consents were obtained from patients participating in the studies and the IRB had oversight of the studies.

E. Evaluation of Financial Disclosure

Financial disclosure information was submitted to the BLA. There was no evidence of financial conflict of interest.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Tc 99m fanolesomab showed a sensitivity of 75%, a specificity of 93% and an accuracy of 88% in a multicenter, single-arm study that enrolled 203 patients with equivocal symptoms and signs of appendicitis. The positive predictive value and negative predictive value were 82% and 90%, respectively.

In a supportive single-arm two-center study, Tc 99m fanolesomab had 89% sensitivity, 68% specificity, 73% PPV and 86% NPV for detection of appendicitis in 56 patients with equivocal symptoms and signs in a supportive single-arm, two-center study.

B. General Approach to Review of the Efficacy of the Drug

The review is a recapitulation of the results of Dr Lindblad review. The reader is referred to that review for detailed discussion of findings and concerns. The principal focus of the review was studies Phase III (Study 98-004) and Phase II (Study 97-003). Other clinical study information was used for safety evaluation.

C. Detailed Review of Trials by Indication

Both studies were designed as open-label and multicenter studies for evaluating the efficacy of Tc 99m Technetium Tc 99m fanolesomab for the detection of appendicitis.

A total of 259 patients with equivocal symptoms and signs of appendicitis defined as absence of one or more of the following (periumbilical pain migrating to right lower quadrant (RLQ), gradual onset of pain, increasing intensity of pain over time, pain aggravated by movement and coughing, McBurney's point tenderness, referred tenderness to RLQ with palpation in other quadrants, abdominal muscular spasm with RLQ tenderness, temperature >101^0 F, white blood cell count > 10,500/mm^3) were enrolled in the two trials.

The phase II study did not explicitly define atypical history /symptoms and absence of McBurney's point tenderness was used as one possible component of an atypical examination, and "normal WBC count" was given as an example of the criterion "atypical laboratory results".

The diagnosis of appendicitis by technetium Tc 99m fanolesomab imaging assessed by blinded readers was compared to a final clinical diagnosis based upon a surgical pathology report (in cases that proceeded to appendectomy) or upon two weeks of follow-up in the phase III and 4 weeks in phase II (in cases without surgical intervention).

The study investigators were not required to rely on technetium Tc 99m fanolesomab imaging for their diagnosis of appendicitis and had access to other diagnostic tests (49 patients had CT scan, 17 had ultrasound, 11 had other modalities). Appendicitis prevalence in the phase 3 study was 30%. The three independent blinded readers were provided with scintigrams presented in a randomized sequence and with patient's gender, age and body habitus, but received no other clinical information. Evaluations are based on the individual reads of the 3-blinded readers and their aggregate. The majority read (at least 2 out of 3 readers agreeing for an individual patient) determined the aggregate.

Image Evaluation

Images were evaluated by site investigators and three experienced blinded nuclear medicine practitioners for the presence or absence of infection and specifically, as "appendicitis" or "no appendicitis" The criteria for a positive scan for appendicitis was abnormal, persistent technetium Tc 99m fanolesomab accumulation within the right lower abdominal quadrant.

Performance Measures

The following primary and secondary performances were measured:

Primary performance outcome measures:

The phase II and phase III studies used the agreement rate as the primary efficacy outcome measures. The primary performance outcome was the rate of agreement between the diagnosis made by the blinded readers and the institutional final clinical diagnosis. Clinical follow up was obtained (2 weeks for the phase III and 4 weeks for the phase II) in the event surgery was not performed.

Secondary performance outcome measures:

The secondary outcome measures included:

- Agreement rates of the individual site investigators assessments of Technetium Tc 99m fanolesomab 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- Technetium Tc 99m fanolesomab imaging questionnaires

In addition both studies evaluated the clinical utility of Technetium Tc 99m fanolesomab with a questionnaire given to surgeons. Prior and after starting the Technetium Tc 99m fanolesomab 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. The choices were

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

The post scan questionnaire was completed after reviewing the results of the Technetium Tc 99m fanolesomab scan, but prior to treatment, and without information from any additional diagnostic tests.

For all patients in the phase III and about half patients (25 of 56) in the phase II, the surgeons were asked to estimate the likelihood of appendicitis using the following categories:

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

A total of 31 of 56 patients in the phase II study had the likelihood of appendicitis estimated using the following categories:

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

In both studies (phase II and III) subjects underwent clinical and laboratory evaluations at enrollment and thorough out the study. Evaluations included history, physical examination and laboratory testing. Patients were observed during the first hour following administration of Tc 99m fanolesomab. Vital signs (blood pressure, pulse and oral body temperature) were taken and recorded immediately prior to administration of Tc 99m fanolesomab and at five minutes, 30 minutes and one-hour post-administration.

Statistical Methods

The binominal distribution was used to establish confidence intervals for all proportions, including accuracy, sensitivity, specificity, PPV and NPV. One sided 95 % confidence intervals for each proportion in the phase III study and two sided 95 % CI in phase II study were specified.

Kappa statistics and concordance rate were used to measure inter observer agreement between the blinded readers. The concordance rate was calculated as the proportion of patients for whom each pair of readers agree.

The potential impact of the imaging study on clinical patient management was assessed by comparing the referring surgeons', intended clinical management course pre scan and post-scan. However, this evaluation did not capture the impact of the imaging study on the actual patient management.

In addition ROC analysis was performed to compare the ROC curves pre- and post-technetium Tc 99m fanolesomab. 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.

Study 1 or (Study 98-004)

Study 98-004 was a pivotal phase III, multicenter study conducted at ten U.S. sites in patients presenting with equivocal signs and symptoms of appendicitis. A total of 203 patients, of both sexes, ages five years and older, were enrolled at 10 hospitals. Subjects included female and male patients, 5 years of age or older, with right lower quadrant (RLQ) abdominal pain, and equivocal presentation of appendicitis. Equivocal presentation was determined by the referring surgeon and included the presence of one or more of the following criteria, Atypical history, physical examination and laboratory findings. This study was designed to assess the efficacy and safety of Tc 99m fanolesomab imaging for detection of acute appendicitis.

The primary efficacy endpoints were sensitivity and specificity of the Tc 99m fanolesomab based on the image assessment of three blinded readers compared with the patient's final institutional diagnosis. Clinical laboratory measurements and vital signs, patients' pre injection measurements were provided baseline values for comparison with post injection values to test for a possible drug effect.

Study 2 (Study 97-003)

Study 97-003, the supporting phase II study, was conducted at two U.S. sites in a total of 56 patients presenting with equivocal signs and symptoms of appendicitis. The objectives of the study were to assess the safety of Tc 99m fanolesomab and efficacy by evaluating the diagnostic accuracy of Tc 99m fanolesomab scintigraphy for the diagnosis of appendicitis and other inflammatory causes of right lower quadrant abdominal pain.

Patients included in both study 1 and study 2 presented with right lower quadrant pain (RLQ) and one or more signs or symptoms that were equivocal for acute appendicitis. These equivocal criteria were:

- 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)

The inclusion criteria in both studies (97-003 and 98-004) were similar except for minor differences.

The phase II study (97-003) enrolled patients who were ≥8 years of age. Patients in the phase III trial (98-004) were 5 years and above. The phase II study did not also explicitly define atypical history /symptoms and atypical examination (absence of McBurney's point tenderness was used as one possible component of an atypical examination), and "normal WBC count" was given as an example of the criterion "atypical laboratory results.

Subjects were excluded from enrollment in both studies for the following reasons:

- Pregnancy or nursing
- Diagnosis of pelvic inflammatory disease (PID)
- History of two or more hospital admissions for abdominal pain of unknown etiology in the past six months
- CT imaging for workup of the current episode of RLQ abdominal pain
- Known sensitivity to murine protein
- Participation in this study or another Technetium Tc 99m fanolesomab study
- Dosing with an investigational drug within 30 days of admission to this study
- Presence of radioactivity in their body that may have interfered with the imaging procedure
- Physical condition unsuitable for radionuclide imaging
- Two week follow up unlikely to be completed,

Dosing

Patients received 10 to 20 mCi (370 to 740 MBq) of Tc 99m containing 75 to 125 µg of fanolesomab. Patients younger than 18 years of age (5-17 years of age) received 0.21 mCi Tc 99m per kilogram of body weight, up to a maximal dose of 20 mCi.

Results

Demography

Table 3 Patient Demographics. Parameters include age, weight, and height, in addition to gender and race.

Characteristics	Phase III Study 98-004	Phase II Study 97-003
Entered	203	56
Eligible for Efficacy evaluation	200	56
Dropped-ineligible	3	0
Dose		
Anti CD-15 IgM AB Dose ug (mean) (range)	120.5 (32.5-250.0)	124.6(87.5-143.7)
Radioactive Dose (mCi): mean (range)	16.0 (4.2-33.0)	14.3 (8.1-19.5)
Age		
Age, mean (min, max)	30.5(5.2-85.9)	29.3 (9.1-77.5)
Pediatrics age (5-17 years)	49 (24%)	15(27%)
Geriatrics (≥ 65 years)	10(5%)	2(4%)
Weight and Height		
Weight mean(min, max)	65.9 (29.5-104.5)	69.2(21.4-127.3)
Height mean (min, max)	162.8 (121.9-193)	165.2(104.1-198.1)
Gender		
Female, no (%)	121(60%)	31 (55%)
Male, no (%)	82 (40%)	25(45%)
Race		
Caucasian	149(73%)	22(39%)
Hispanic	32 (16%)	28(50%)
Black	16(8%)	3(5%)
Oriental	-	2(4%)
Filipino	-	1(2%)
Other	6(3%)	0
Equivocal Presentation of Appendicitis		
Atypical history and/or symptoms	148 (73%)	34(61%)
Atypical physical examination	138(68%)	18(32%)
Fever less than 101^0 F	185(91%)	44(79%)
Atypical lab results	115(57%)	21(38%)
Study Sites	10 sites	2 sites
Incidence of Appendicitis	59(30%)	28(50%)

Study 1 or (Study 98-004)

Primary Performance

The primary performance was based on 200 patients. Fifty-nine (29.5%) of the 200 patients had a final Institutional diagnosis of appendicitis.

The primary performance of Tc 99m fanolesomab in study one is summarized in table 4.

Table 4: Blinded Read Performance in the phase 3 study (N=200)

SENSITIVITY				
EVALUATION	N (+)	TP	Sensitivity	95% Confidence Interval
Aggregate	59	44	75	62,85
SPECIFICITY				
EVALUATION	N(-)	TN	Specificity	95% Confidence Interval
Aggregate	141	131	93	87,97
ACCURACY				
EVALUATION	N (T)	TP+TN	Accuracy	95% Confidence Interval
Aggregate	200	175	88	82,92
POSITIVE PREDICTIVE VALUE				
EVALUATION	TP + FP	TP	PPV	95% Confidence Interval
Aggregate	54	44	82	69,91
NEGATIVE PREDICTIVE VALUE				
EVALUATION	TN + FN	TN	NPV	95% Confidence Interval
Aggregate	146	131	90	84,94

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".
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

The technetium Tc 99m fanolesomab read by the blinded readers had higher specificity and negative predictive value.

Secondary Performance

The secondary performance measurements include a sensitivity, specificity, accuracy and PPV and NPV of site Investigators for diagnosis of appendicitis, disposition plan, likelihood of appendicitis and blinded reader concordance.

The secondary performance measures of Tc 99m fanolesomab in study 1 are summarized below:

Site Investigators

Table 5.Sensitivity, Specificity, Accuracy and PPV and NPV of Site Investigators for Diagnosis of Appendicitis (N=200)

EVALUATION	N(+)	TP	SENSITIVITY	LL of 95% CI
Aggregate	59	53	90	81
	N(-)	TN	**SPECIFICITY**	LL of 95% CI
Aggregate	141	122	87	81
	N(t)	TP + TN	**ACCURACY**	LL of 95% CI
Aggregate	200	175	88	83
	TP + FN	TP	**PPV**	LL of 95% CI
Aggregate	72	53	74	64
	TN + FN	TN	**NPV**	LL of 95% CI
Aggregate	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".
N (-) is total number of patients with a final institutional diagnosis of "no acute appendicitis".
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

Accuracy was about the same as blind read accuracy. However the site investigators read the image for sensitivity and correspondingly lower specificity.

Disposition Plan

Table 6. Phase 3 Shifts in Intended Management /Disposition

Pre-scan Disposition	Post-scan Disposition			
	Send Home	Admit for Observation	Surgery	Pre total
Final Diagnosis of 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 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

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

Medical Reviewer Comments:

Tc 99m fanolesomab resulted a shift to better management as is seen especially in those patients whose initial disposition was admit for observation. Patients were safely sent home, fewer were admitted for observation, and some could go directly to surgery.

The conclusions that can be drawn from these findings are limited for the following reasons: lack of blinded randomized comparison group, use of additional diagnostic studies in a subgroup of patients, lack of confirmation beyond the completion of the questionnaire that the surgeon's intent to shift management was actually implemented.

Likelihood of Appendicitis

In both trials surgeons were asked to estimate the likelihood of appendicitis. The likelihood estimates of appendicitis versus the surgeons' pre and post scan estimate is summarized in the table below:

Table 7: Phase 3 likelihood of Appendicitis versus the Surgeon's Pre-scan Likelihood Estimate

	Post-Tc 99m fanolesomab Study					
Pre-Tc 99m Technetium Tc 99m fanolesomab 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	3	1	1	1	3	9
Indeterminate appendicitis	0	0	0	5	10	15
Probably appendicitis	0	1	0	7	16	24
Definitely appendicitis	0	0	0	0	7	7
Post-Total	3	2	1	13	36	55
Final Diagnosis No Acute Appendicitis						
Almost definitely not appendicitis	20	1	0	1	0	22
Probably not appendicitis	33	13	2	1	0	49
Indeterminate appendicitis	24	10	7	4	0	45
Probably appendicitis	6	5	1	2	3	17
Definitely appendicitis	0	0	0	1	0	1
Post-Total	83	29	10	9	3	134

As it is shown in the Table 7: (Compare numbers in "pre-Total" column with numbers in "Post-Total" row) the surgeon's post-scan likelihood estimates were more consistent with the true incidence of appendicitis than the pre-scan estimates within this study population.

Medical Reviewer Comment

Compared to pre-scan likelihood estimates shifts towards the true estimates occurred within the pre scan likelihood range of >20 - <80%. Note that three patients judged to be "probably not" appendicitis shifted to "almost definitely not" appendicitis post-scan. Also three patients without appendicitis shifted to "definitely appendicitis" post scan.

Table 8 compares the pre-scan estimate with the actual incidence of appendicitis.

Table 8: Phase 3 Incidence of Appendicitis versus the Surgeon's Pre-scan Likelihood Estimate

Surgeon's pre-scan likelihood estimate	N	Incidence
80-100%	8	88%
60-79%	44	61%
40-59%	65	25%
20-39%	61	15%
0-19%	22	0%

Medical Reviewer Comment:

The surgeon's pre-scan likelihood estimates correlated with the true incidence of appendicitis within this study population. Patients in the high likelihood end of the spectrum (80-100% group) had a lower incidence of atypical presentation compared to patients in the low likelihood spectrum.

Agreement among Blinded Readers

The results of the Tc 99m fanolesomab blinded readers were evaluated for agreement using the kappa statistic and concordance rate (the rate of agreement between readers).

Table 9: Phase 3 Blinded Reader Concordance

PAIRS OF BLINDED READERS	CONCORDANCE RATE, (95% CI)	KAPPA STATISTIC (95% CI)
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)

Concordance rates were 0.88 to 0.90 and kappa statistics was moderate with value of 0.54 and 0.55.

Likelihood Ratio having appendicitis

The pre scan and the post scan probability of having appendicitis likelihood ratio was calculated using the following formula:

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.

The likelihood ratios show that a positive scan increases the probability of having appendicitis, and a negative scan decreases the probability. Patients whose images were evaluated as positive for appendicitis had estimates of a likelihood of having appendicitis 6 to 13 times greater post-test than estimates of 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 fanolesomab study is positive. For images evaluated as negative for appendicitis, the odds that a patient has appendicitis decrease by a factor 1/5 to 1/3 of their pre-test likelihood. Given the aggregate blind read results, a negative Tc 99m fanolesomab study decreased the odds that a patient had appendicitis by a factor of approximately ¼. (See table 10)

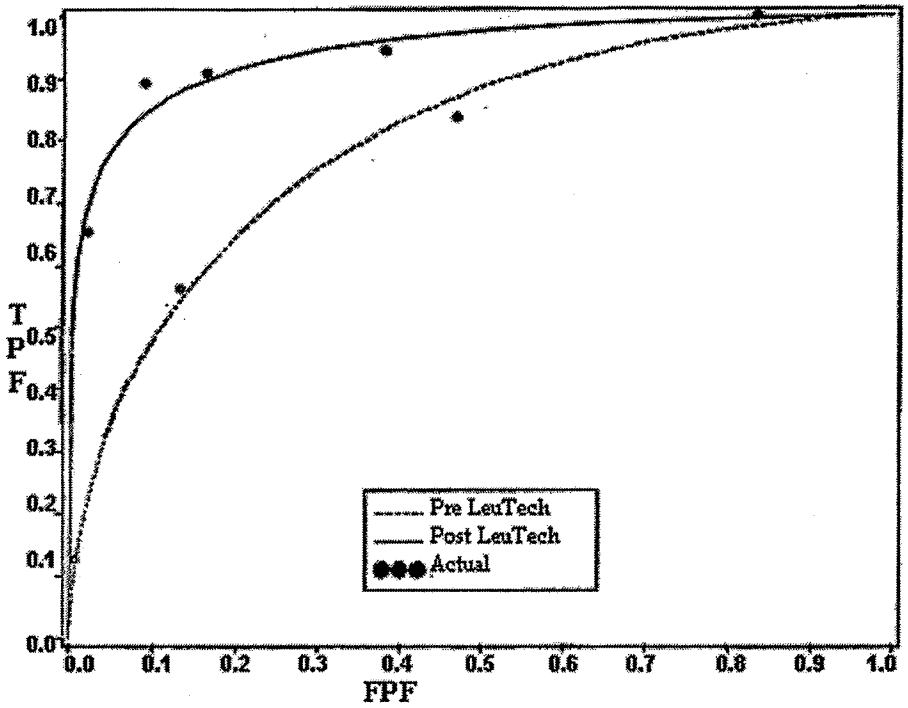
Table 10: Phase 3 Likelihood Ratios having appendicitis

Evaluation	LR (+)	95% CI	LR (-)	95% CI
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 Read	10.52	(5.68, 19.46)	0.27	(0.18, 0.43)

Receiver Operator Characteristics (ROC) Analysis

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 was evaluated using the ROC curves.

The post-scan curve was 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 (+)] was greater than the pre-scan TPF, while for any given TPF; the post-scan FPF was less than the pre-scan FPF. As demonstrated in the figure 1, the post-scan curve that indicates 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%) (See Figure 1).



ROC Curves Pre and Post LeuTech Scan

TPF = Sensitivity FPF = 1-Specificity

Figure 1. Receiver Operator Characteristics (ROC) Analysis

Study 2 or Study 97-003

Primary Performance Results

The primary performance was assessed in 56 evaluable patients. Of 56 patients 28 patients (50%) had a final institutional diagnosis of appendicitis. The primary performance of Tc 99m fanolesomab in study 2 is summarized in Table 11.

Table 11: Phase 2 Blinded Reader: Technetium Tc 99m fanolesomab Images, Appendicitis/No Appendicitis

EVALUATION	N(+)	TP	Sensitivity	95% Confidence Int.
AGGREGATE	28	25	89	(71, 95)
EVALUATION	**N(-)**	**TN**	**Specificity**	**95% Confidence Int.**
AGGREGATE	28	19	68	(48, 82)
EVALUATION	**TP + FP**	**TP**	**PPV**	**95% Confidence Int.**
AGGREGATE	34	25	74	(55, 86)
EVALUATION	**TN + FN**	**TN**	**NPV**	**95% Confidence Int.**
AGGREGATE	22	19	86	(64, 94)

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".
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

Secondary Performance Results

The secondary performance measurements include sensitivity, specificity, accuracy and PPV and NPV of site Investigators for diagnosis of appendicitis, disposition plan, likelihood of appendicitis and blinded reader concordance.

The secondary performances of Tc 99m fanolesomab in the study2 are summarized below:

Site Investigators

Table 12. Patient-Based Agreement Rate, Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value Of Technetium Tc 99m fanolesomab Images with Final Institutional Diagnosis, Appendicitis/No Appendicitis.

AGREEMENT RATE	NT	TP+ TN	Agreement Rate (%)	95% Confidence Int.
Combined	56	49	88	(75, 94)
SENSITIVITY	N(+)	TP	Sensitivity	95% Confidence Int.
Combined	28	27	96	(80, 97)
SPECIFICITY	N(-)	TN	Specificity	95% Confidence Int.
Combined	28	22	79	(59, 90)
POSITIVE PREDICTIVE VALUE	TP + FP	TP	Positive Predictive Value	95% Confidence Int.
Combined	33	27	82	(64, 91)
NEGATIVE PREDICTIVE VALUE	TN +FN	TN	Negative Predictive Value	95% Confidence Int.
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".
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

Changes in Disposition Plan

Two patients would have been sent home prior to Technetium Tc 99m fanolesomab scanning, and none after Technetium Tc 99m fanolesomab 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% (4/56).

Table 13 Phase 2 Shifts in Management /Disposition

Pre-scan Disposition	N	Post-scan Disposition	N	Patients with Appendicitis #	(%)
Home	6	Home	4	0	0%
		Observation	0	0	0%
		Surgery	2	2	100%
Observation	38	Home	13	0	0%
		Observation	9	3	33%
		Surgery	16	15	96%
Surgery	12	Home	2	0	0%
		Observation	0	0	0%
		Surgery	10	8	80%

Likelihood of Appendicitis

In both trials surgeons were asked to estimate the likelihood of appendicitis. In the first half of the phase 2 study, the intended clinical management plans was assessed using a different questionnaire (table 14 and 15). The second half of the study had methods of estimating the likelihood of appendicitis similar to the phase III trial.

The phase II study evaluations of the likelihood of appendicitis demonstrated a positive shift in a surgeon's confidence in the diagnosis of appendicitis after using Technetium Tc 99m fanolesomab.

a) First half of study

Table 14: Phase 2 Distribution Of Confidence In Intended Clinical Management Pre- And Post-Technetium Tc 99m fanolesomabStudy, N = 31*

Pre-Tc 99m Technetium Tc 99m fanolesomab Study	Post-Tc 99m Technetium Tc 99m fanolesomab 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%)
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 description was in protocol.

b) Second half of study

The second half of the study used a questionnaire similar to that of the phase III trial.

Table 15: Phase 2 Distribution of Estimates of Likelihood of Appendicitis Pre- and Post-Technetium Tc 99m fanolesomab Study, N = 25*

	Post-Tc 99m Technetium Tc 99m fanolesomab Study					
Pre-Tc 99m Technetium Tc 99m fanolesomab 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

Agreement among Blinded Readers

The results of the Tc 99m Technetium Tc 99m fanolesomab blinded readers were evaluated for agreement using the kappa statistic and concordance rate (the rate of agreement between readers).

Table 16 Phase 2 Measures of Inter-Reader Agreement for Diagnosis of Appendicitis/No Appendicitis.

Reader Comparisons	Concordance, (95% CI)	Kappa Statistic, (95% CI)
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)

Concordance rates ranged from 0.77 to 0.80 and kappa statistics ranged from 0.34 to 0.45.

Management

Table 17 describes patients who had surgery, but ultimately were not diagnosed with appendicitis.

Table 17: Phase 2 Patients Undergoing Surgery Whose Final Diagnosis was Negative for Appendicitis.

PT.	FINAL DIAGNOSIS	INVESTIGATOR READ OF Tc 99m Tc 99m fanolesomab 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.

Subgroup analysis

The primary efficacy parameters were evaluated in several subgroups of patients. These subgroups are broken down into the atypical appendicitis patient population subgroups:

- Entry Criteria
- Pre-scan disposition plan

- Pre-scan likelihood estimate

This will be followed by other patient populations including:

- Patients based on their WBC counts
- Women between 14-35y
- Pediatric: 5-9y and 10-17y
- Geriatric >65y
- "Other infections"
- Patients who also had CT scans performed

The sponsor investigated other sub-populations, which will be briefly discussed. These include populations based on:

- Age group
- Gender
- Race
- Weight (BMI)
- Enrollment order

Entry Criteria

As discussed previously, the entry criteria were broken down into the number of positive criteria for an individual patient, and the incidence of appendicitis. The performance of the scan in these groups and the 2-6 positive entry criteria is shown below. This is presented for the aggregate blind read in the evaluable patient population. As was shown earlier, there are only minor differences from the intent to treat and the evaluable groups, and the onsite and blinded readers group (Table 18).

Table 18: Phase 3 Performance Based on Number of Positive Entry Criteria

# of Positive Entry Criteria	N	TN	TP	FN	FP	Incidence	Sensitivity	Specificity	PPV	NPV
1	14	4	8	2	0	71%	80	100	100	67
2	38	19	9	7	3	42%	56	86	75	73
3	31	19	10	2	0	39%	83	100	100	90
4	45	31	10	2	2	27%	83	94	83	94
5	33	23	4	2	4	18%	82	67	85	50
6	25	22	3	0	0	12%	100	100	100	100
7	10	9	0	0	1	0%	*	90	*	100
8	3	3	0	0	0	0%	*	100	*	100
9	1	1	0	0	0	0%	*	100	*	100
Total	200	131	44	15	10	30%	75	93	82	90
2-6	172	114	36	13	9	29%	73	93	80	90

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

Table 19: Phase 3 Performance Based on Number of Positive Major Entry Criteria

# of Positive Major Entry Criteria	N	TN	TP	FN	FP	Incidence	Sensitivity	Specificity	PPV	NPV
1	16	6	8	2	0	63%	80	100	100	75
2	53	24	17	9	3	49%	65	89	85	73
3	69	47	15	3	4	26%	83	92	79	94
4	62	54	4	1	3	8%	80	95	57	98
Total	200	131	44	15	10					

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

Removing those patients that had only one positive entry criterion or as many as 7, 8, or 9 positive criteria did not alter the performance of the scan significantly (Table 19).

Pre-scan disposition Plan

Another group of patients that reflect an atypical appendicitis population is the group for whom the pre-scan disposition would be admission for observation. The performance of the scan in this subgroup is presented below (Table 20).

Table 20: Phase 3 Performance Based on Pre-scan Disposition Plan

Disposition	N	TN	TP	FN	FP	Incidence	Sensitivity	Specificity	PPV	NPV
Home	44	37	3	2	2	11%	60	95	60	95
Surgery	35	10	20	3	2	66%	87	83	91	77
Observation	121	84	21	10	6	26%	68	93	78	89

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

The admit for observation group has a slightly lower incidence of appendicitis than the overall population, a lower sensitivity, but the specificity and NPV are maintained.

Pre-scan likelihood estimate

The performance of the scan using the surgeon's pre-scan likelihood estimates is displayed below (Table 21).

Table 21: Phase 3 Performance Based on Surgeon's Pre-scan Likelihood Estimate

Surgeon's pre-scan likelihood estimate	N	TN	TP	FN	FP	Incidence			Sensitivity	Specificity
						TOTAL	If scan + (PPV)	If scan – (100%NPV)		
0-19%	22	22	0	0	0	0%	-	-	-	100%
20-39%	61	51	6	3	1	15%	86%	6%	67%	98%
40-59%	65	43	12	4	6	25%	67%	8%	75%	88%
60-79%	44	14	20	7	3	61%	86%	33%	74%	82%
80-100%	8	1	6	1	0	88%	100%	50%	86%	100%

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

Though the numbers are small, the higher the predicted likelihood of appendicitis, the greater the incidence of appendicitis despite a negative scan.
If the scan is negative but there is a high clinical suspicion of appendicitis, the true incidence of appendicitis could be up to 50%.

Patients based on WBC counts

The WBC count is of interest for two reasons. First, the WBC count was the entry criteria that most closely correlated with the surgeon's pre-scan likelihood estimate, and as will be shown below, it correlates with the actual incidence of appendicitis. Secondly, this scan tags neutrophils and may therefore be dependent on the number of neutrophils at a given site of inflammation and indirectly on the number of circulating neutrophils.

The performance of the scan is broken down into subcategories of patients with low or elevated WBC counts. This is based on the blind aggregate read.

Table 22: Phase 3 Performance Based on the WBC Count

WBC (/mm3)	N	Incidence	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
4,000 - 7,000	38	11%	32	1	3	2	25	94	33	91
7,000 - 10,000	67	10%	56	5	2	4	71	93	56	97
10,000 - 15,000	57	46%	29	18	8	2	69	94	90	78
15,000 - 20,000	28	54%	11	14	1	2	93	85	88	92
> 20,000	10	70%	3	6	1	0	86	100	100	75

TN is the number of true negative outcomes, TP is the number of true positive outcomes, FN is the number of false negative outcomes, FP is the number of false positive outcomes,PPV is the positive predictive value, NPV is the negative predictive value

As is shown, the incidence of appendicitis climbs as the WBC count rises (Table 22). The sensitivity is low with a low WBC but there were only 4 cases of appendicitis. Specificity was well maintained.

Women between 14-35y

Women during reproductive years always present a diagnostic challenge when presenting with lower abdominal pain. Within this study it is important to remember that pregnancy and PID were both exclusion criteria. The performance is presented for the aggregate blind read and those women between 14-35y with a surgical pre-scan likelihood of 20-79% (Table 23).

Table 23: Phase 3 Performance in Women 14 – 35 y

	N	Incidence	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
Women 14-35y 20-79% Likelihood	52	19%	40	8	2	2	80%	95%	80%	95%

Pediatric: 5-9y and 10-17y

The pediatric data is presented from pooled phase 2 and phase 3 data. The studies have comparable eligibility criteria and performance determinations based on three blinded readers as has been outlined. Pooling this data allows a greater number of patients to be assessed. These data are presented for the aggregate blind read from the phase2 and 3 studies (Table 24).

Table 24: Pooled Phase 2 and Phase 3 Performance in Pediatrics

Age	N	Incidence	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
5-9y	15	47%	8	6	1	0	86%	100%	100%	89%
10-17y	48	27%	32	11	2	3	85%	92%	82%	93%

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

In the 5-9y group, the incidence of appendicitis was high and the number of patients low despite pooling the data.

Geriatric >65y

The geriatric data is also pooled across the phase 2 and 3 studies. The data is presented for the aggregate blind read.

Table 25: Pooled Phase 2 and Phase 3 Performance in Geriatrics

	N	Incidence	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
Geriatric >65	12	50%	5	6	0	1	100%	83%	86%	100%

As in the pediatric data, the number of patients is small and the incidence of appendicitis is high.

"Other infections"

Patients with a final institutional diagnosis of "other infection" included diverticulitis, cholecystitis, gastroenteritis, urinary tract infections and many more. Some of these were surgical cases and some were not. These cases were examined in order to look at the performance of the scan in patients without appendicitis but with another type of infection or inflammation. These data are also pooled data across the phase 2 and 3 studies and will be presented for both the onsite reads and the aggregate blind reads.

Table 26: Pooled Phase 2 and Phase 3 Performance in Patients with a Final Institutional diagnosis of "Other Infection"

	N	Incidence	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
Onsite reads	30	0%	21	0	0	9	-	70%	-	100%
Aggregate blind	30	0%	17	0	0	13	-	57%	-	100%

There were 33 patients with a final institutional diagnosis of "other infection". Three of these patients had appendicitis and other infections and were therefore not included in this analysis.

For the onsite group, 4 of 9 patients with a final diagnosis of other infection and a false positive read for appendicitis went to surgery. The final diagnosis and disposition is listed below.

Table 27: Phase 2 and Phase 3 Onsite Read - Final Diagnosis and Disposition in Patients with a Diagnosis of "Other Infection"

Site	Patient #	Diagnosis	Surgery
		Phase 2 study	
B	3	Crohn's/Gastroenteritis	No
B	7	PID/Ileitis	No
		Phase 3 Study	
A	5	UTI	No
A	15	Ruptured Bladder	Yes
A	21	Peri-appendicitis	Yes
A	34	Enteritis	No
B	12	Ovarian CA/Abscess	Yes
C	3	Crohn's	Yes
I	8	Gastroenteritis	No

Only one of the four patients that went to surgery may not have needed surgery. This was the patient A-21 with periappendicitis but no evidence of actual appendicitis. This was a pathology reading.

For the Aggregate blind read, there is an increase in the number of false positive readings. Patient B-12, which was read as a false positive by the onsite readers, was not read as a false positive by the blinded aggregate read.

Table 28: Phase 2 and Phase 3 Aggregate Blind Read - Final Diagnosis and Disposition in Patients with a Diagnosis of "Other Infection"

Site	Patient #	Diagnosis	Surgery
		Phase 2 study	
A	36	Colitis	No
B	3	Crohn's/Gastroenteritis	No
B	7	PID/Ileitis	No
		Phase 3 Study	
A	5	UTI	No
A	15	Ruptured Bladder	Yes
A	21	Peri-appendicitis	Yes
A	23	Colitis	No
A	31	Diverticulitis	No
A	34	Enteritis	No
C	3	Crohn's	Yes
H	34	Ruptured Diverticulum	Yes
I	8	Gastroenteritis	No
J	9	Colonic Mass	Yes

For the aggregate blind read, 5 of the FP read patients went to surgery. Other than A 21 as previously discussed, all had reasonable indications for surgery. For both the onsite readers and the aggregate blind read there is a high rate of false positive reads in those patients that ultimately had another site of infection or inflammation other than appendicitis. This is of critical importance clinically when interpreting positive scans in the possible presence of other infections. As demonstrated by the cases from these studies, a positive scan alone was not an adequate indication to take a patient to surgery, but was used in context with all the available clinical data.

The sponsor also looked at "other infections". This was based on how the scans were read. The scans were primarily read as positive or negative. If the scan was positive, the reader would decide based on predefined criteria if the scan was positive for appendicitis or positive for another infection. This study was not designed to demonstrate the performance of the scan in patients with abdominal infections of any source, but was designed to look at specifically atypical appendicitis. The performance of the scan in patients with abdominal infections which includes those with appendicitis is shown in the table below. The onsite read is based on the elimination of the first two cases (considered training cases) at all but the lead site (9 out of 10 sites).

Table 29: Phase 3 Performance in Patients with Tc 99m fanolesomab Scan Results of "Other Infection"

Phase 3	N	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
Onsite reads	182	89	69	7	17	91	84	80	93
Aggregate blind	200	117	60	22	1	73	99	98	84

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

***Reviewer comment**: This study was neither powered nor adequately designed to determine the significance or utility of Tc 99m fanolesomab at identifying abdominal infections vs. no infections.*

The ability to identify what type of infection, and the small number of patients with infections other than appendicitis contributes 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 Tc 99m fanolesomab in the diagnosis of patients with abdominal pain and any type of infectious etiology.

CT scans

Within the phase III study, 49 patients underwent CT scanning in addition to having had their Tc 99m fanolesomab scan. The table below depicts the outcomes of Tc 99m fanolesomab 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 as only positive or negative reads with no middle ground. Given these issues and that this study was not designed to compare CT to Tc 99m fanolesomab, the performance of Tc 99m fanolesomab relative to CT scanning in these 49 patients is not interpretable.

Table 30: Comparison of Tc 99m fanolesomab and CT results, (N=49)

	CT				
Tc 99m Tc 99m fanolesomab Tm	**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

Table 31: Performance of Tc 99m fanolesomab vs. CT Scan

N=49	Tc 99m fanolesomab	CT Scan
Sensitivity	83	67
Specificity	86	89
Accuracy	88	84
PPV	67	67
NPV	94	89

Reviewer comment: Performance parameters were calculated on this small subset of patients. These data are not interpretable. This trial was not adequately powered or designed to meaningfully study and compare these two imaging agents.

Distribution of Planned diagnostic procedures relative to Tc 99m fanolesomab scanning

Surgeons were asked both prior to and after the Tc 99m fanolesomab scan what further diagnostic testing would they perform. These data are depicted below.

Table 32: Distribution of Planned diagnostic procedures relative to Tc 99m fanolesomab scanning

	N	PATIENTS %
Prior to Tc 99m Tc 99m fanolesomab Tm		
Conventional CT	28	15
Spiral CT	17	9
Ultrasound	17	9
Barium Enema	2	1
Other	9	5
After Tc 99m Tc 99m fanolesomab Tm		
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).

Age Group

The following table shows the performance outcome measures for the various age groups from the phase 3 study.

Table 33: Sensitivity and Specificity-Subgroups: 5-17,18-64, >65 Years, Evaluable Patients.

SENSITIVITY									
	5 - 17 yr			18 - 64 yr			65 yr		
	N(+)	TP	Sens.	N(+)	TP	Sens.	N(+)	TP	Sens.
Aggregate	11	8	73	44	32	73	4	4	100
Investigators	10	9	90	40	37	93	4	3	75
SPECIFICITY									
	5 - 17 yr			18 - 64 yr			65 yr		
	N(-)	TN	Spec.	N(-)	TN	Spec.	N(-)	TN	Spec.
Aggregate	37	35	95	98	91	93	6	5	83
Investigators	35	31	89	87	74	85	6	5	83
ACCURACY									
	5 -17 yr			18 - 64 yr			≥65 yr		
	N(T)	TP+TN	Acc.	N(T)	TP+TN	Acc.	N(T)	TP+TN	Acc.
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
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
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.

Medical officer Comment: *The performance outcome measures in various age groups were similar.*

Comparison of Gender Subgroups:

Table 34 compares gender using all evaluable patients.

Table 34 Comparisons of Gender Subgroups, Evaluable Patients.

SENSITIVITY						
	FEMALE			MALE		
	N(+)	TP	Sensitivity	N(+)	TP	Sensitivity
Blinded Reader Aggregate	30	25	83	29	19	66
Investigators	27	25	93	27	24	90
SPECIFICITY						
	FEMALE			MALE		
	N(-)	TN	Specificity	N(-)	TN	Specificity
Blinded Reader Aggregate	91	87	96	50	44	88
Investigators	82	71	87	46	39	85

Medical Officer Comment:

Breaking the data down into gender subgroups revealed no differences in the performance parameters.

Comparison of Race Subgroups:

Table 35: Comparison of Race Subgroups, Evaluable Patients.

SENSITIVITY						
	WHITE			ALL OTHER		
	N(+)	TP	Sensitivity	N(+)	TP	Sensitivity
Blinded Reader Aggregate	44	32	73	15	12	80
Investigators	41	36	88	13	13	100
SPECIFICITY						
	WHITE			ALL OTHER		
	N(-)	TN	Specificity	N(-)	TN	Specificity
Blinded Reader Aggregate	103	96	93	38	35	92
Investigators	93	80	86	35	30	86

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.

Medical Officer Comment: *No significant differences by race within this phase 3 study were found.*

Comparison of BMI Subgroups:

Table 36 shows patient subgroups based on weight.

Table 36: Comparison of BMI Subgroups, Evaluable Patients.

SENSITIVITY						
	BMI < 27			BMI ≥ 27		
	N(+)	TP	Sensitivity	N(+)	TP	Sensitivity
Blinded Reader Aggregate	42	32	76	15	10	67
Investigators	39	37	95	13	10	77
SPECIFICITY						
	BMI < 27			BMI ≥27		
	N(-)	TN	Specificity	N(-)	TN	Specificity
Blinded Reader Aggregate	96	88	92	45	43	96
Investigators	85	75	88	43	35	82

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.

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. 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.

Enrollment Order

Table 37 shows the comparison of patients by the order in which they presented.

Table 37: Enrollment Order

APPENDICITIS					
FIRST 5 PATIENTS			OTHER PATIENTS		
N(+)	TP	Sensitivity	N(+)	TP	Sensitivity
11	9	82	48	44	92
N(-)	TN	Specificity	N(-)	TN	Specificity
37	30	81	104	92	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.

There was a trend towards improvement in comparing the first 5 patients enrolled to the subsequent patients. 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.

Summary of Subgroup Analyses

Although the individual entrance criteria were not able to differentiate equivocal appendicitis in a consistent manner, the sum of 2-6 positive atypical findings provided a better atypical appendicitis population. The surgeon's management questionnaire also provided an important tool to select a sub-population based on disposition plan and likelihood of appendicitis that could reasonably be considered atypical. Each of these major subgroups had performance data that were comparable to the overall population.

Other subgroups including patients based on their WBC count, women between 14-35, pediatric and geriatric populations all showed similar performance data. The women were selected for not having PID in the phase 3 study, and as shown in the data from those patients diagnosed with other infections, the performance may not differentiate PID from appendicitis well. The accuracy of the scan in women who may have PID is not clear.

Medical Officer Comment: *General age group, gender, race, weight (based on BMI) and enrollment order yielded no significant drop off in performance.*

Pooled Analyses of Data

Both the phase two and phase three trials were conducted under similar protocols. They used the same Technetium Tc 99m fanolesomab dose. Both protocols sought to enroll patients with atypical signs and symptoms of appendicitis, though the phase II study had a 50% rate for 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.

$$\text{Pooled} = \frac{w2P2 + w3P3}{w2 + w3}$$

P2= diagnostic measure phase II
P3= diagnostic measure phase III

w2 and w3 are there associated weights provided by the inverse of the measure's variance.

Demographic Characteristics:

The demographic characteristic and distribution of atypical sign and symptoms in the two studies were similar. The pooled data are shown below:

Table 38: Phase 2 and 3 Summary Statistics for Age, Weight, Height and BMI

	N	MIN.	MAX.	MEAN	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

Table 39: Phase 2 and 3 Distribution of Gender and Race

		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**

Final Institutional Diagnosis:

Table 40: Phase 2 and 3 Distribution of Final Institutional Diagnosis for Appendicitis/No Appendicitis and Infection/No Infection, Evaluable Patients

	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.		

Performance:

The performance evaluation of the pooled data compares the aggregate blinded readers and the pooled onsite investigators. The data results are affected by the larger phase III trial. The sensitivity is greater for the onsite investigators, and the specificity is greater for the aggregate blind readers.

Table 41: Phase 2 and 3 Sensitivity, Specificity, Accuracy, PPV and NPV of Blinded Readers' Evaluations of Tc 99m Technetium Tc 99m fanolesomab Images for Appendicitis/No Appendicitis, Evaluable Patients

EVALUATION				
SENSITIVITY	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.

Likelihood Ratios

The likelihood ratios are similar in the pooled data to those in the phase 3 trial.

Table 42: Phase 2 and 3 Likelihood Ratios of Tc 99m Technetium Tc 99m fanolesomab Images For Appendicitis/No-Appendicitis, Evaluable Patients

EVALUATION	LR(+)	95% CI	LR(-)	95% CI
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.				

Management:

The management of patients is reflected in the questionnaires that were filled out both before and after the Technetium Tc 99m fanolesomab 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 44.

Clinical Management Disposition

The total number of patients from the polled data includes 189 patients from the phase 3 study and 56 patients from the phase 2 study.

Table 43: Phase 2 and 3 Distribution of Intended Clinical Management Decisions Prior to and Following Tc 99m Technetium Tc 99m fanolesomab Imaging, Evaluable Patients

Pre-scan Disposition	N	Post-scan Disposition	N	Patients with Appendicitis #	(%)
Home	49	Home	40	2/40	(5%)
		Admit Obs.	2	0/2	(0%)
		Surgery	7	5/7	(71%)
Admit Obs.	151	Home	52	0/52	(0%)
		Admit Obs.	52	7/52	(14%)
		Surgery	47	40/47	(85%)
Surgery	45	Home	7	0/7	(0%)
		Admit Obs.	2	0/2	(0%)
		Surgery	36	29/36	(81%)

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 Technetium Tc 99m fanolesomab scan.

Table 44: Phase 2 and 3 Distribution of Estimates of Likelihood of Appendicitis Pre- and Post-Tc 99m Technetium Tc 99m fanolesomab Evaluable Patients

	Post-Tc 99m Technetium Tc 99m fanolesomab Study					
Pre-Tc 99m Technetium Tc 99m fanolesomab 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

Subgroup Analysis:

As in the phase 3 data already presented, there are no significant differences noted in the pooled data with regard to subgroups based on age, gender, race or weight. The only additional subgroup of patients that will be presented are those that received antibiotics. A suspicion that antibiotics may affect the sensitivity of the scan based on treating the infection could be raised. In patients that received antibiotics within 24 hrs there was a fall off in the specificity, not the sensitivity, for both the onsite readers and the blinded offsite readers. These data are presented below.

Table 45: Phase 2 and 3 Comparison of Antibiotic Use Subgroups, Evaluable Patients

SENSITIVITY						
	ANTIBIOTICS			NO ANTIBIOTICS		
	N(+)	TP	Sensitivity	N(+)	TP	Sensitivity
Blind-Read Aggregate	12	11	89	75	58	80
Site Investigators	12	11	92	70	65	93
SPECIFICITY						
	ANTIBIOTICS			NO ANTIBIOTICS		
	N(-)	TN	Specificity	N(-)	TN	Specificity
Blind-Read Aggregate	24	19	80	145	131	94
Site Investigators	22	15	68	134	117	87

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.

The sensitivity for subgroups according to antibiotic usage was comparable and specificity appeared to be higher for patients not taking antibiotics, both for the aggregate blind-read results (13% higher) and for the site investigators (19% higher).

The prevalence of appendicitis was the same (about one third of patients) for patients taking antibiotics and for patients not taking antibiotics. However, the prevalence of other infections was three times higher for patients taking antibiotics. The numbers are shown below:

Table 46. The prevalence of appendicitis for patients taking antibiotics and not taking antibiotics

Final Institutional 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 (this data was presented in the performance section of the phase 3 study):

- 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 were read as false positive by the blind read aggregate
- 12% of negative patients were 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.

Reviewer Comments: *These analyses are based on a very small sample size.*

D. Summary of Integrated Efficacy

The primary performance of technetium Tc 99m fanolesomab in the phase III trial had sensitivity of 75%, a specificity of 93% and an accuracy of 88% for a diagnosis of appendicitis. The positive predictive value and negative predictive value were 82% and 90%, respectively. For investigators at the clinical sites, scintigraphy with technetium Tc 99m fanolesomab had a sensitivity of 91% and a specificity of 86%. Accuracy was 87%. The positive predictive value and negative predictive value were 73% and 96%, respectively.

In the phase III trial, 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 1/5 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.

At the phase II trial where 50% of the patients had a final institutional diagnosis of appendicitis scintigraphy with technetium Tc 99m fanolesomab had a sensitivity of 89%, a specificity of 68% for a diagnosis of appendicitis. The positive predictive value and negative predictive value were 74% and 86%, respectively.
For investigators at the clinical sites, scintigraphy with technetium Tc 99m fanolesomab had a sensitivity of 96% and a specificity of 79%. Accuracy was 88%. The positive predictive value and negative predictive value were 82% and 96%, respectively.

The likelihood ratios that a positive scan increases the probability of having appendicitis, and a negative scan decreases the probability. Concordance rates was 0.77 to 0.80 and kappa statistics of 0.34 to 0.45.

E. Efficacy Conclusions

The review supports approval of Tc 99m fanolesomab for diagnosis of equivocal appendicitis based on the two clinical trials (phase II and phase III).

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The data for safety was obtained from 14 trials where 523 patients were exposed to Technetium Tc 99m fanolesomab. All patients received a single injection of Tc 99m Technetium Tc 99m fanolesomab, except for the 30 patients enrolled in Study 99-001, who received two injections of decayed Technetium Tc 99m fanolesomab to evaluate

HAMA response. Thirty patients enrolled in Study 97-001 received a single injection of decayed Technetium Tc 99m fanolesomab to evaluate HAMA response. The average antibody dose was 121 ug (range 32.5 ug to 250 ug). Excluding the patients who received decayed Technetium Tc 99m fanolesomab in studies 97-001 and 99-001, the radioactive dose ranged from 1.1 mCi to 33.0 mCi, with a mean of 15 mCi.

Thirty-seven of the 523 patients (7%) who received technetium Tc 99m fanolesomab reported a total of 49 adverse events (AEs). Of the 49 AEs reported, 4 (8%) were classified as severe: (pain, decrease in O2 saturation (68%) with chest pressure, sepsis and hypotension). Two of the 4 severe adverse events were serious adverse events (sepsis and hypotension) and were accompanied by death. The two deaths relationship to study treatment is considered to be unlikely based on time course and pre-existing condition.

Overall, the studies reviewed indicate that Tc 99m fanolesomab is safe for use in patients 5 –96 years of age to diagnose appendicitis in patients presenting with atypical signs and symptoms.

B. Description of Patient Exposure

523 patients were exposed to the product both within the company's appendicitis indication development program and in other studies.

Table 47: Safety Extent of Exposure

Number Of Patients	All Patients in All Studies	All Patients in Palatin IND Studies	All Patients in Phase 2 and 3 Appendicitis Studies
Entered (Male/Female)	523 244/279	407 177/230	259 107/152
Received Study	523	407	259
Eligible for Safety Evaluations	523	407	259
Age (yr.): Mean (Range)	37.7 (5-91)	38.3 (5-91)	29.7 (5-85)
Anti-CD15 IgM Antibody Dose (ug): Mean (Range)	121 (N=493) (32.5-250.0)	122 (32.5-250)	121.4 (32.5-250)
Anti-CD15 IgM Antibody Dose (ug/kg): Mean (Range)	1.8 (N=471) (0.6-4.2)	1.8 (N=406) (0.7-4.2)	1.9 (N=259) (0.8-4.2)
Radioactive Dose (mCi): Mean (Range)	14.7 (N=457) (1.1-33.0)	15.4(N=377) [1] (4.2-33)	15.6 (4.2-33)

[1] Radioactive dose was not administered to 30 patients in study 99-001

Demographics

Demographic summary of patients who have received the product is listed below.

Table 48: Safety Demographic Summary

		All Patients In All Studies	All Patients in Palatin IND Studies	All Patients in Phase 2 and Phase 3 Appendicitis Studies
Age (Years)	N	523	407	259
	Minimum	5	5	5
	Maximum	91	91	85
	Median	35	35	26
	Mean	37.7	38.3	29.7
	SD	19.4	20.9	16
Age Category N (%)	5-11	29(5.5)	28 (6.9)	26 (10)
	12-16	32(6.1)	31 (7.6)	30 (11.6)
	17-64	398(76.1)	287 (70.5)	191 (73.7)
	> 65	64(12.2)	61 (15)	12 (4.6)
Gender N (%)	Female	279(53.3)	230 (56.5)	152 (58.7)
	Male	244(46.7)	177 (43.5)	107 (41.3)
Race N (%)	White	319(61)	294 (72.2)	171 (66)
	Black	49(9.4)	34 (8.4)	19 (7.3)
	Hispanic	98(18.17)	64 (15.7)	60 (23.2)
	Other	24(4.6)	15 (3.7)	9 (3.5)
	Not specified	33(6.3)	0	0
Height (cm)	N	434	404	257
	Minimum	104.1	104.1	104.1
	Maximum	200.7	200.7	198.1
	Median	167.6	167.6	166.4
	Mean	163.3	166.3	164.7
	SD	13.3	13.5	14.4
Weight (kg)	N	494	406	259
	Minimum	21.4	21.4	21.4
	Maximum	172.4	172.4	127.3
	Median	70.5	72.0	67.3
	Mean	72.8	73.1	68.5
	SD	22.1	22.0	20.2
Body Mass Index (BMI)	N	434	404	257
	Minimum	12.6	12.6	12.6
	Maximum	61.3	61.3	46.7
	Median	25.1	25.2	24.2
	Mean	26.1	26.1	24.9
	SD	6.3	6.3	5.6

Patients enrolled in the clinical studies ranged in age from 5 to 91 years, with an average age of 37. 7 years. Twenty-nine (29; 5.5%) patients were between 5 and 11 years old, 32 (6.1 %) were between 12 and 16 years, 398 (76.1 %) were between 17 and 64 years, and 64 (12.2%) were 65 or older.

Two hundred seventy-nine (53.3%) patients were female and 244 (46.7%) were male. There were 319 (61.0%) Whites, 49 (9.4%) Blacks, 98 (18.7%) Hispanics, and 24 (4.6%) "Other"; race was not specified for 33 patients. Weight ranged from 21.4 kg to 172.4 kg, with an average of 72.8 kg. Body mass index (BMI; subject weight in kg divided by squared subject height in meters) ranged from 12.6 to 61.3, with an average of 25.1. Height ranged from 104.1 cm to 200.7 cm, with an average of 166.3 cm.

The age range and category distribution, gender, race, height, weight and BMI ranges were similar across the three groupings.

***Reviewer Comment**: The majority of subjects (398 or 76%) enrolled in these studies were females. more than one-half (61%) were whites and 9 % of the patients were blacks.*

C. Methods and Specific Findings of Safety Review

The safety data for each study were examined separately to check for consistency of findings across studies. No study specific safety findings were identified. The pooled data were also examined and are presented below.

Deaths, Serious Adverse Events and Discontinuations

There were two deaths and 3 serious AEs (pain, sepsis and hypotension). Two of the 3 serious adverse events (sepsis and hypotension) were accompanied by death.

Death 1

Patient C-02 was a 66-year-old white male who was enrolled in study 99-006 (phase 2, post surgical abscess) became hypotensive 7 hrs post injection of Tc 99m fanolesomab followed by cardiac and respiratory arrest. The patient expired 9 hours post injection after unsuccessful resuscitation attempts.

The patient past medical history included insulin-dependent diabetes mellitus, hypertension, hyperlipidemia, chronic anemia, retinopathy, neuropathy and renal failure due to diabetic nephropathy, rheumatic fever. The patient was admitted to the hospital to rule out sepsis or (b) (6) after a three-day history of nausea, vomiting, fever and chills following peritoneal dialysis catheter removal following catheter site infection. His medications on admission included NPH insulin 8 units BID, one aspirin 81 mg per day, Zestril 10 mg per day and Lipitor 10 mg per day, and a permanent cardiac pacemaker.

Patient received an intravenous injection of 0.5mL of Tc 99m fanolesomab (Lot Number 0882-23- 47414B) 09:25 or (b) (6) His vital signs were monitored and were stable during the imaging period. He completed the imaging study without incident. At approximately 16:30, the patient became less responsive and hypotensive and was transferred to ICU for observation. At 16:50, the patient became obtunded. He was coded for approximately 35 minutes without response and was declared dead due to cardiac and respiratory arrest at 17:30.

Based upon clinical history and autopsy results, the cause of death was reported to be congestive heart failure. The autopsy results indicated the patient had mild cardiomegaly with left ventricular hypertrophy, fibrinous pericariditis with 200 mL of serosanguinous pericardial effusion, atelectasis and congestion of both lower lung lobes and chronic passive congestion of the liver.

Death 2:

Patient 1012 was a 35 years old female who was enrolled in study LT-006-02 (phase 2, post –surgical infection). This patient presented to the emergency department in acute shortness of breath following 2 days history of increasing coughing and productive sputum. At the time of arrival to emergency department she was found to have a pulse oximetry of 84% and tachypnea. The patient was placed on mechanical ventilation for hypoxia. The chest x-ray that was performed in the emergency department showed bilateral pulmonary edema and questionable pneumonia.

The patient was managed for bronchospasm with Combivent inhalation, Lasix,Tequin and Vancomycin, IV fluid. The patient also received treatment for IDDM, decubitus ulcer of the left foot and pancreatitis and hypotension. The subject condition deteriorated and the patient died one week following Tc 99m fanolesomab administration.

Medical Reviewer Comment:

The relationship death 2 to study treatment is remote based on pre-existing condition. However, the time course in the first patient (Death I) who became hypotensive 7 hrs post injection of Tc 99m fanolesomab and later died due to cardiac and respiratory arrest is concerning. Even though the patient had multiple pre-existing conditions that could lead to death, it would be difficult to exclude the contribution by Tc 99m fanolesomab.

Adverse Event Summary

The summary includes safety information for 523 patients who received technetium Tc 99m fanolesomab. Except 30 patients who received multiple doses of technetium Tc 99m fanolesomab, all others received a single dose of Tc 99m fanolesomab.

Thirty-seven of the 523 patients (7%) who received technetium Tc 99m fanolesomab reported a total of 49 adverse events (AEs). Of the 49 AEs reported, 4 (8%) were classified as severe: (pain; chest pressure and decrease in oxygen saturation; sepsis; hypotension). Two of the 4 severe adverse events were serious adverse events and were accompanied by death. Thirty-five (71.4%) AEs were classified as mild in severity and 10 (20,4%) were moderate.

Action was taken for 5 AE s (dizziness; weakness; syncope; chest pressure and decrease in pO2; each involved a change in body position (place to supine position) to resolve the event. All AEs had resolved by the end of the study period.

Overall Adverse Events

The most frequently reported AE was flushing, experienced by 10 patients (1.9%). Dyspnea was reported by 5 (1.0%) patients. Dizziness and paresthesia were reported in 3 patients (0.6%) each. Nausea, chest pressure, pain, nasopharyngitis, headache, hypotension and syncope were reported in 2 patients (0.4%) each. All 10 cases of flushing were considered possibly or probably related to the study drug, as were 3 cases of dyspnea, 2 cases of chest pressure sensation, and single cases of nausea, injection site burning, injection site erythema, PO2 decreased, dizziness, headache, paresthesia, contusion and hot flushes.

Adverse events are summarized by MedDRA term and body system on the next page.

Table 49. Safety Summary Of Adverse Events by MedDRA Term and Body System.

Body System	MedDRA term	All Patients (Patients=523) N (%)	All Patients in Palatin IND Studies (N=407) N (%)	All patients in Phase 2 and Phase 3 Studies (N=259) N (%)
All Systems	ANY EVENT	37(7)	35(8.6)	20 (7.72)
Gastrointestinal Disorders	ANY EVENT	4(0.76)	4(0.98)	1(0.39)
	Diarrhea	1(0.19)	1(0.25)	1(0.39)
	Nausea	2(0.38)	2(0.49)	0
	Toothache	1(0.19)	1(0.25)	0
General Disorders and administration site condition	ANY EVENT	7(1.34)	5(1.23)	3(1.16)
	Chest Pressure Sensation	2(0.38)	2(0.49)	1(0.39)
	Ill defined disorders	1(0.19)	1(0.25)	0
	Injection Site Burning	1(0.19)	1(0.25)	1(0.39)
	Pain Non Specific	2(0.38)	0	0
	Weakness	1(0.19)	1(0.25)	1(0.39)
Infections and Infestations	ANY EVENT	3(0.57)	3(0.74)	0
	Nasopharyngitis	2(0.38)	2(0.49)	0
	Sepsis nos	1(0.19)	1(0.25)	0
Injury Poisoning and Procedural Complication	ANY EVENT	2(0.38)	2(0.49)	0
	Joint Sprain	1(0.19)	1(0.25)	0
	Laceration	1(0.19)	1(0.25)	0
Investigations	ANY EVENT	1(0.19)	1(0.25)	0
	PO2 decreased	1(0.19)	1(0.25)	0
Musculoskeletal System Disorders	ANY EVENT	1(0.19)	1(0.25)	0
	Arthralgia Aggravated	1(0.19)	1(0.25)	0
Nervous System Disorders	ANY EVENT	10(1.91)	10(2.46)	7(2.7)
	Dizziness	3(0.57)	3(0.74)	2(0.77)
	Headache nos	2(0.38)	2(0.49)	2(0.77)
	Syncope	2(0.38)	2(0.49)	2(0.77)
	Parasthesia	3(0.57)	3(0.74)	1(0.39)
Respiratory System Disorders	ANY EVENT	6(1.15)	6(1.47)	5(1.93)
	DYSPNEA nos	5(0.96)	5(1.22)	4(1.54)
	Nasal congestion	1(0.19)	1(0.25)	1(0.39)
Skin and Subcutaneous Tissues Disorders	ANY EVENT	1(0.19)	1(0.25)	0
	Contusion	1(0.19)	1(0.25)	0
Vascular Disorders	ANY EVENT	13(2.48)	13(3.19)	10(3.86)
	Flushing	10(1.91)	10(2.46)	9(3.47)
	Hot Flushes nos	1(0.19)	1(0.25)	1(0.39)
	Hypotension	2(0.38)	2(0.49)	0
Total Number of Events		39	28	9

Medical Reviewer Comment:

Vascular disorders were the most common adverse events. Of the total of 37 (7%) patients with adverse events 13 had vascular disorders (flushing, hot flushes and hypotension) classified as vascular. These events occurred at the time of administration of the product to 7 hours post injection period and are judged to be related to the product.

Time of onset ranged from immediately post-injection to 4-½ days post- injection and duration ranged from 1 minute to 4 hours in cases where onset and duration were specified (excluding LT-006-02, subject 1012 who had a pre-existing condition of sepsis).

Severity of AEs was classified as mild, moderate or severe. Of the 49 AEs reported, 4 (8%) were classified as severe: (Chest pressure and decrease in oxygen saturation; pain; sepsis and hypotension). Two of the 4 severe adverse events were serious and were accompanied by death. Neither of the deaths was considered related to Tc 99m Technetium Tc 99m fanolesomab. Thirty-five (71.4%) AEs were classified as mild in severity and 10 (20,4%) were moderate.

Sixteen patients (3.2% of 523 patients) experienced a total of 24 AEs that were considered possibly or probably related to the study drug. The events included all 10 cases of flushing, 3 cases of dyspnea, 2 cases of chest pressure sensation, and single cases of nausea, injection site burning, injection site erythema, PO2 decreased, dizziness, headache, paresthesia, contusion and hot flushes. In 19 (3.6%) patients the 23 AEs were not considered to be related with the study drug.

Safety Summary Of Adverse Events by COSTART Term and Body System.

For comparison of the MedDRA tem and body system with COSTART method, the table below from previous submission has been added.

Consistent to the MeDRA term, the COSTART method demonstrated that the most frequently reported AE was vasodilatation, experienced by 11 (3 %) subjects. Dyspnea was reported by 4 (1%) subjects and paresthesia was reported by 3 (1%) subjects. Headache, pain, pain at injection site, syncope, pharyngitis and dizziness were reported in 2 (1%) subjects each. Asthenia, injection site reaction, malaise, abdominal pain, chest pain, diarrhea, ecchymosis, joint disorder and rhinitis were reported in 1 (<1%) of subjects.

Reviewer Comment: *in general, the two methods (COSTART and medDRA) yielded consistent results.*

Adverse Events Summarized by Common Syndrome

The adverse events are summarized by the common potential clinical syndromes and are presented below in table 55.

Table 50: Incidence of Adverse Events in all of the Patients Receiving Tc 99m fanolesomab (N = 523)

	Number of Subjects Total Subjects 523 N	Incidence %
Infusion Reaction/Allergic Reaction	**25**	**4.7%**
Flushing,	10	1.9%
Dyspnoea	5	0.95%
Syncope	2	0.38%
Dizziness	2	0.38%
Nausea	1	0.19%
Headache	1	0.19%
Hypotension	2	0.38%
Parasthesia	2	0.38%
Injection Site Reaction	**1**	**0.19%**
Injection Site Burning and Erythema	1	0.19%
Others	**11**	**2.1**
Sepsis	1	0.19%
Weakness	1	0.19%
Nasal congestion	1	0.19%
Arthralgia aggravated	1	0.19%
Contusion	1	0.19%
Ill defined Disorders	1	0.19%
Tooth ache	1	0.19%
Nasopharyngitis	1	0.19%
Laceration	1	0.19%
Pain	2	0.38%

The Safety Summary of Moderate or Severe Adverse Events is presented below in table 55.

Table 51: Safety Summary of Moderate or Severe Adverse Events.

MedDRA term	All Patients in All Studies N=523)	All Patients in Palatin IND Studies N=407	All patients in phase 2 and 3 Appendicitis Studies (N=259) N (%)
Chest Pressure	1	1	0
Pain nos	1		0
Sepsis	1	1	0
Laceration	1	1	0
Po2	1	1	0
Arthralgia	1	1	0
Headache	2	2	2
Parasthesia	1	1	0
Dyspnea	1	1	0
Flushing	1	1	1
Hypotension	1	1	0
Weakness	1	1	1
Number of Patients	11 (2.1%)	10 (2.45%)	4 (1.54%)
Total Number of Events	13	12	4

Of the 49 adverse events, 24 in 16 patients were considered possibly or probably related to study drug (relationship was not specified for 2 events). They are summarized below.

Table 52. Safety Summary of Adverse Events Considered Possibly or Probably Related To Study Drug by MedDRA Term and Body System.

MedDRA term	All Patients in All Studies N=523)	All Patients in Palatin IND Studies N=407	All patients in phase 2 and 3 Appendicitis Studies (N=259) N (%)
Nausea	1	1	0
Chest Pressure	2	2	1
Injection Site Burning	1	1	1
Injection Site Erythema	1	1	1
Contusion	1	1	0
PO2 Decreased	1	1	0
Dizziness	1	1	1
Headache	1	1	1
Parasthesia	1	1	1
Dyspnea	3	3	2
Flushing	10	10	9
Hot Flushes	1	1	1
Number of Patients	16 (3%)	16(4%)	12 (5%)
Number of Events	24	24	18

Vital Signs

Changes In Vital Signs From Baseline

Vital signs were measured in 441 patients from 11 of the clinical trials. The vital signs (systolic and diastolic blood pressure, pulse rate and percent oxygen saturation) were assessed at varying time points depending on the study, but in most cases they were measured immediately pre-injection and at 5 minutes, 30 minutes and 1 hour post-injection.

For studies under Palatin INDs, clinical significance of changes in vital signs was defined in the protocols as any change (increase or decrease) that met any of the following criteria:

systolic blood pressure > 35 mm Hg diastolic blood pressure > 25 mm. Hg
pulse rate > 20 beats per minute

The frequency of clinically significant changes from baseline is summarized below.

Table 53: Safety Incidence of Clinically Significant Changes in Vital Signs By MedDRA.

Type of Vital Sign Change Post-Injection	All Patients in All Studies[1] (N = 441) N (%)	All Patients in Palatin IND Studies N=380) N (%)	Multiple Injection (N =258 Patients) N (%)
Blood Pressure Decreased	5(l)	4(l)	2(0.8)
Blood Pressure Increased	5(1)	5(1.3)	3(1.2)
Pulse Rate Decreased	6(1.4)	5(1.3)	4(1.6)
Pulse Rate Increased	6(1.4)	6(1.6)	5(1.9)

[1]Vital signs were not collected for patients in Study 97-001 and were not available for patients in the Gratz-Becker study

Across all studies, 22 patients experienced protocol-defined clinically significant changes in vital signs from baseline values. Of 441 patients with vital sign data both pre- and post-injection, protocol-defined changes were observed as follows: 6 (1.4%) experienced a significant decrease in heart rate and 6 (1.4%) experienced a significant increase in heart rate; 5 patients (1%) experienced a significant decrease in blood pressure and 5 patients (1%) experienced a significant increase in blood pressure.

Medical Reviewer Comment:

The incidence of clinically significant vital signs changes was similar for all three subject-groups. The changes in blood pressure, pulse rate, respirtory rate, oxygen saturation and body temperature were small and non clinically significant during post injection follow up.

Clinical Laboratory Assessments

Clinical laboratory measurements were obtained from 284 patients. In the phase1 clinical pharmacology study, 10 normal volunteers had hematology, chemistry and urinalysis parameters pre-injection and at 1 hour, 4 hours and 18-24 hours post-injection. In addition, white blood cell (WBC) counts and differential assessments were performed at 3, 5.5 10, 15, 30 and 45 minutes post-injection. In both the phase 3 appendicitis study with 203 patients and in a phase 2 osteomyelitis study of 24 patients, hematology and chemistry parameters pre-injection and at 2 hours post-injection were obtained. In the Phase I repeat-injection HAMA study 30 normal volunteers had hematology and chemistry parameters measured immediately prior to each injection and at 7 days and 28 days after the second injection. , Study 99-003 (Phase 2 prosthetic joint infection) and study 99-004 (Phase 2 diabetic foot ulcer) measured hematology and chemistry parameters pre-injection and 3 - 4 hours post-injection.

Laboratory Parameters with Clinically Significant Changes from Baseline

In each of the studies, study investigators were to evaluate post-injection changes in clinical laboratory parameters from baseline for clinical significance.
A total of 7 clinically significant changes in laboratory parameters were reported in 4 of 284 patients (1.4 %) enrolled in the studies. The change in LDH in Subject 1-03 (Study 97-002) was determined to be a laboratory error. The changes in AST and ALT in Patient D-21 (Study 98-004) and in hemoglobin (Hgb) and hematocrit (Hct) in Patient H-10 (Study 98-004) were attributed to disease. The only subject who experienced clinically significant changes in laboratory parameters possibly attributed to Technetium Tc 99m fanolesomab was Subject A-25 in Study 99-001. This subject experienced an elevation in AST (3 fold)and LDH (7 fold) one week after the second injection. Values for both measurements returned to normal range at 4 weeks following the second injection .The investigator noted that this elevation was unexpected and clinical and laboratory follow-up revealed no cause.

Clinical Laboratory Parameters: Range Shifts

Clinical laboratory measurements post-injection were categorized according to each laboratory's normal range as low (less than the lower limit), normal (within the normal range), or high (greater than the upper limit). In Study 98-004 (Phase 3 Appendicitis) and Study 98-005 (Phase 2 Osteomyelitis), laboratory measurements were performed 2 hours post-injection. A summary of the findings from the phase II (Osteomyelitis study) and phase III (appendicitis study) study is provided below.

Table 54: Safety Statistically Significant Shifts in Laboratory Parameters at 2 Hours, All Patients in Phase 3 Appendicitis and Phase 2 Osteomyelitis Studies

Parameter	Number of Patients with Shift[1]	Shift Upward		Shift Downward		
		Low to Normal	Normal to High	Normal to Low	High to Normal	High to Low
Hematology						
WBCs	33 (N=184)	2	5	5	21	0
Neutrophils	37 (N=144)	5	4	6	21	1
Hemoglobin	27 (N=184)	6	1	20	0	0
Clinical Chemistry						
Total Protein	27 (N=171)	2	0	16	8	1
BUN	18 (N=188)	2	0	13	3	0

[1]N is total number of patients in shift table, i.e., patients with both baseline and 2-hour measurements.

A total of 33 patients had a shift in WBCs and, the downward shift was from high to normal for 21 patients, from normal to low for 5 patients, from normal to high for 5 patients and from low to normal for 2 patients.

The shift in neutrophils was from high to normal for 21 patients, from normal to low for 6 patients, from normal to high for 4 patients and from low to normal for 5 patients. Considering the 27 patients having a shift in hemoglobin, the shift was from normal to low for 20 patients, from low to normal for 6 patients, and from normal to high for one subject. For each parameter, there was a significantly higher incidence of downward shifts post-injection. Considering the 27 patients with a shift in total protein, the shift was from normal to low for 16 patients, from high to normal for 8 patients, from high to low for 1 subject, and from low to normal for 2 patients. For the 18 patients having a shift in BUN the shift was from normal to low for 13 patients, from high to normal for 3 patients and from low to normal for 2 patients.

The drop in WBC count was transient and the recovery was in 1 hour. This data had numerous values that were unreported or not obtained. There was a drop in the total WBC, which appears to be driven by the drop in the total neutrophil count. This was a transient drop with a recovery in 1 hours. The worse individual case started with a WBC of 3.8×10^3/uL and an absolute neutrophil count of 1.4×10^3/uL. This neutrophil count dropped to a low of 0.05×10^3/uL at 45 min then started to recover though the 4 hr and 18-24 hr data are not reported. Similar downward shifts in WBCs and granulocytes were observed for the Phase 1 study in 10 normal volunteers (Study 97-002) during the first

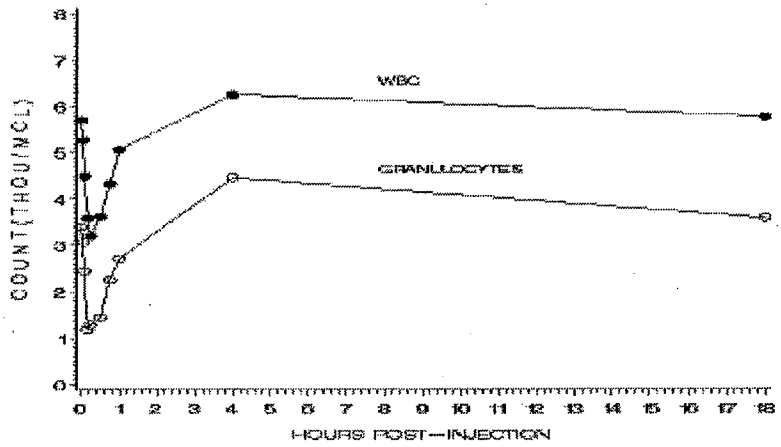
30 minutes post- injection. Upward shifts in the relative percent of lymphocytes and monocytes were also noted in this time period, and could be attributed to the reduction in absolute granulocyte count.

Table 55: Safety WBC, Granulocyte and Lymphocyte Counts Phase 1 Study

Parameter	Baseline	3 min	5 min	10 min	15 min	30 min	45 min	1 hr	4 hr	18-24 hr
WBC(10^3/uL)	5.7	5.1	4.3	3.6	3.2	3.6	4.2	5.1	5.2	-
Granulocytes(%)	57%	-	52%	39%	35%	34%	45%	47%	-	-
Granulocytes(10^3/uL)	3.3		2.2	1.4	1.1	1.2	1.9	2.4	-	-
Lymph(%)	31%	33	37%	48%	51%	47%	41%	41%	-	33%
Lymph(10^3/uL)	1.8	1.7	1.6	1.7	1.6	1.7	1.7	2.1	-	-
Worse Individual Cases Reported (Patient # 4 - 21y F)										
WBC(10^3/uL)	3.8	3.7	3.6	3.2	2.4	2.5	2.5	3.0	4.3	4.3
Granulocytes(%)	38%	25%	24%	20%	12%	6%	2%	5%	-	-
Granulocytes(10^3/uL)	1.4	0.9	0.9	0.6	0.3	0.2	0.05	0.2	-	-
Lymph(%)	53%	64%	67%	67%	76%	76%	86%	84%	-	-
Lymph(10^3/uL)	2.0	2.4	2.4	2.1	1.8	1.9	2.2	2.5	-	-
Patient # 7 – 36 F										
WBC(10^3/uL)	3.8	-	-	2.4	2.3	2.2	2.4	2.8	4.9	4.5
Granulocytes(%)	52%	-	-	31%	14%	15%	14%	30%	-	48%
Granulocytes(10^3/uL)	2.0	-	-	0.7	0.3	0.3	0.3	0.8	-	2.2
Lymph(%)	31%	-	-	52%	60%	58%	64%	60%	-	37%
Lymph(10^3/uL)	1.2	-	-	1.2	1.3	1.3	1.5	1.7	-	1.7

There were fewer shifts at 1 hour and by 4 hours there was no evidence of downward shifts. (See Figure 3 below).

Figure 2. Mean changes in WBC and Granulocytes Count as a function of Time Following Tc99m Technetium Tc 99m fanolesomab Administration (N=10, study 97-002)



Some changes in laboratory parameters have been thought to be caused by increases in hydration from intravenous fluids given in a hospital emergency room or diagnostic imaging area. The investigator did not consider these transient shifts clinically meaningful. No other shifts in hematology parameters were statistically significant

Overall, the clinical laboratory parameter changes were small and none of the changes were considered to be clinically significant. No change, other than those of WBCs and neutrophils, was thought to represent a treatment-related trend, and changes for WBCs and neutrophils were of a small magnitude in this non-neutropenic patient population.

Reviewer comment: *There are no data on the performance of technetium Tc 99m fanolesomab in neutropenic patients. This issue was raised and noted in the Medical Imaging and Device Advisory Committee. The two patients with the lowest WBC were both in a phase 1 trial and both had significant drops in their absolute neutrophil count. Though this affect appears to be transient, further study will be required to assess the safety and performance of this product in neutropenic patients.*

Human Anti-Mouse Antibody (HAMA) Response

1. HAMA Response Following Single Injection

HAMA response following single injection of Technetium Tc 99m fanolesomab was evaluated in total of 54 patients in three trials. 20 of the 54 patients were enrolled in Study 98-004 (Phase 3 appendicitis). 30 additional patients were evaluated in Study 97-001 (clinical pharmacology, 30 normal volunteers) and 4 patients in Study 95-001.

Blood samples were obtained prior to injection of Technetium Tc 99m fanolesomab and at 3 weeks to 4 weeks post-injection.

Patients in Studies 97-001 and 95-001 were re-tested at 3 months to 4 months for HAMA response. Patients in Study 98-004 who had a positive response at 3 weeks to 4 weeks were to be re-tested for HAMA response at 12 weeks to 16 weeks post-injection..

No patients had a positive HAMA response at baseline and at any time-point tested.

HAMA Response Following Multiple Injections

Evaluation of HAMA response following two injections of Technetium Tc 99m fanolesomab administered three weeks apart was evaluated in 30 normal volunteers (Study 99-001).

A baseline control serum sample was collected from each subject, followed by the first Technetium Tc 99m fanolesomab injection. Approximately 3 weeks later, another serum sample was collected followed by the second Technetium Tc 99m fanolesomab injection. One week and 4 weeks after the second Technetium Tc 99m fanolesomab injection, additional serum samples were collected from each subject. Any serum sample collected post- Technetium Tc 99m fanolesomab administration having a HAMA titer greater than or equal to 4X the baseline value (prior to the first Technetium Tc 99m fanolesomab administration) for the same subject was considered positive.

Five (16.7%) of the 30 patients exhibited positive HAMA responses at one or more post-injection times and they are presented below.

Medical Officer Comment:

The data on clinical significance of the HAMA assay is limited. The incidence of antibody development in patients receiving Technetium Tc 99m fanolesomab has not been adequately determined because the assay was not directly quantitative and its ability to detect low titers could not be assured.

COMPARISON OF SAFETY BY SUBGROUPS

This summary of compression of safety (adverse events, vital signs, change in laboratory parameters) by subgroups was made by age, gender, race, WBC counts, renal impairment, hepatic impairment, antibiotics, NSAIDs, opioids, analgesics and antipyretics, psychotherapeutic agents, faneolesomab dose.

No overall differences in safety (adverse events, vital signs, change in laboratory parameters) were observed in subgroups by age, gender, race, WBC counts, renal impairment, hepatic impairment, antibiotics, NSAIDs, opioids, analgesics and antipyretics, psychotherapeutic agents and faneolesomab dose.

D. Safety Conclusions

Safety data were summarized for 523 patients enrolled and dosed in 14 trials. Patients ranged in age from 5 years to 91 years, with an average age of 38 years. Twenty-nine of 523 patients (5.5%) were between 2 and 11 years old, 32 (6.1%) were between 12 and 16 years old, 398 (76.1%) were between 17 and 64 years, and 64 (12.2%) were 65 or older. Two hundred seventy-nine patients (279; 53.3%) were female and 244 (46.7%) were male. There were 319 (61.0%) whites, 49 (9.4%) blacks, 98 (18.7%) Hispanics, and 24 (4.6%) "other".

All patients received a single injection of Technetium Tc 99m fanolesomab, except for the patients enrolled in Study 99-001, who received two injections of decayed Technetium Tc 99m fanolesomab to evaluate HAMA response. Patients enrolled in Study 97-001 received a single injection of decayed Technetium Tc 99m fanolesomab to evaluate HAMA response.

Patients in the clinical development program received an average dose of 0.48 mL (range 0.13 to 1.00 mL), containing an average of 121ug (range 32.5 to 250 ug) of anti-CD 15 IgM antibody. Excluding patients in Studies 97-001 and 99-001 (who received decayed Technetium Tc 99m fanolesomab), the dose of radioactivity ranged from 1.1 to 33.0 mCi (mean = 14.7 mCi).

Serious adverse events and subsequent death occurred in two patients enrolled in clinical trials included in this summary. One subject became hypotensive 6 hr 50 min post-injection, followed by cardiac and respiratory arrest; resuscitation attempts were unsuccessful. Another subject had a diagnosis of sepsis prior to the administration of Technetium Tc 99m fanolesomab. The subject's condition deteriorated during the hospital course, and the subject died one week following Technetium Tc 99m fanolesomab administration. Neither SAE was considered related to Technetium Tc 99m fanolesomab by the investigators. No patients discontinued study participation due to any AEs.

Thirty-seven of 523 patients (7 %) reported a total of 49 AEs. Time of onset ranged from immediately post-injection to 4 days 11 hours and 53 minutes post- injection and duration ranged from 1 minute to 4 hours in cases where onset and duration were specified. Sixteen patients (3.2% of 523 patients) experienced a total of 24 AEs that were considered possibly or probably related to the study drug.

The most frequently reported AE was flushing, experienced by 10 patients (2 %). Dyspnea was reported by 5 (1%) patients. Dizziness and paresthesia were reported in 3 patients (0.6%) each. Nausea, chest pressure, pain, nasopharyngitis, headache, hypotension and syncope were reported in 2 patients (0.4%) each. All 10 cases of flushing were considered possibly or probably related to the study drug, as were 3 cases of dyspnea, 2 cases of chest pressure sensation, and single cases of nausea,

injection site burning, injection site erythema, PO_2 decreased, dizziness, headache, paresthesia, contusion and hot flushes.

Of the 49 AEs reported, 4(8%) were classified as severe: pain, decrease in pO2 and chest pressure, sepsis, and hypotension. Thirty-five (71%) AEs were classified as mild in severity and 10 (20%) were moderate. Severity was not specified for one subject with abdominal pain (2%).

For 441 patients with vital sign data available at both the pre- and post-injection time points, protocol-defined changes were observed as follows: 6 patients (1.4%) experienced a significant increase in heart rate (change> 20 bpm) and 6 patients (1.4%) experienced a significant decrease; 5 patients (1.1%) experienced a significant increase in blood pressure and 5 patients experienced a significant decrease (systolic change> 35mmHg and/or diastolic change> 25 mmHg). The incidence of clinically significant vital signs changes (blood pressure, pulse rate, respiratory rate, oxygen saturation and body temperature) were small and non clinically significant during post injection follow up.

Clinical laboratory parameters were evaluated for changes from baseline for the patients in six of the studies. One subject experienced changes in AST and LDH (3 to 7 fold respectively) one week after the second injection of Technetium Tc 99m fanolesomab.

Changes in neutrophil and WBC values comprised the largest numbers of patients experiencing a negative or a positive shift in laboratory parameters. Twenty-six of 188 patients (13.8%) and 28 of 151 patients (18.5%) in Studies 98-004 and 98-005 combined demonstrated a negative shift at 2 hours post- Technetium Tc 99m fanolesomab administration in WBCs and neutrophils, respectively. However, of 26 shifts downward for WBC count (versus 7 shifts upward), 21 of them were shifts from an above-normal pre- injection value to a normal post-injection value. Similarly for neutrophils, of 28 shifts downward (versus 9 shifts upward), 21 of them were from an above-normal pre-injection value to a normal post-injection value. These shifts were not unexpected as Tc 99m fanolesomab is known to bind rapidly to polymorphonuclear neutrophils.

Human antimouse antibody (HAMA) response following a single fanolesomab administration was evaluated in a total of 54 subjects. None of the subjects had a positive HAMA response at either 3-4 weeks post-injection (54 subjects evaluated) or at 3-4 months post injection (34 of the 54 subjects evaluated). However, five of 30 patients (16.7%) had HAMA measurements following two injections of fanolesomab. The incidence of antibody development in patients receiving Technetium Tc 99m fanolesomab has not been adequately determined because the assay was not directly quantitative and its ability to detect low titers could not be assured.

No significant age, gender or race-related differences were noted in the incidence of AEs, clinically significant changes in laboratory parameters or clinically significant changes in vital signs. There were no AEs or clinically significant changes in either clinical laboratory or vital sign data in the 8 patients presenting with WBCs below the lower limit of normal. One of 9 patients presenting with renal impairment reported a clinically significant vital sign change and one of 3 patients presenting with hepatic impairment had an AE (injection site burning and erythema).

E. Adequacy of Safety Testing

The methods (vital signs, clinical laboratory parameters including HAMA assay) used to monitor safety in both trials were adequate. However, the assay used to determine antibody development in patients receiving Technetium Tc 99m fanolesoma was not directly quantitative and its ability to detect low titers could not be assured.

F. Summary of Critical Safety Findings and Limitations of Data

There data reviewed had no critical safety findings. Although, a relatively small database it deemed sufficient to adequately characterize the safety profile of this product. The safety analyses conducted by the applicant and FDA resulted in similar conclusions.

VIII. Dosing, Regimen, and Administration Issues

In 14 trials, 523 patients were exposed to Technetium Tc 99m fanolesomab. All patients received a single injection of Tc 99m Technetium Tc 99m fanolesomab, except for the 30 patients enrolled in Study 99-001, who received two injections of decayed Technetium Tc 99m fanolesomab to evaluate HAMA response. Thirty patients enrolled in Study 97-001 received a single injection of decayed Technetium Tc 99m fanolesomab to evaluate HAMA response.

The average antibody dose was 121 ug (range 32.5 ug to 250 ug). Excluding the patients who received decayed Technetium Tc 99m fanolesomab in studies 97-001 and 99-001, the radioactive dose ranged from 1.1 mCi to 33.0 mCi, with a mean of 15 mCi.

Technetium Tc 99m fanolesomab has no been studied in children < 5 years of age and there is no enough experience with repeat dosing. Murine monoclonal antibodies are frequently immunogenic.The development of human anti-mouse antibodies (HAMA) can alter the pharmacokinetics, biodistribution, safety and imaging performance properties of the administered agent. The incidence of antibody development in patients receiving Technetium Tc 99m fanolesomab has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers.

Fanolesomab is not intended for direct administration to the patient without reconstitution and labeling with Sodium Pertechnetate Tc 99m Injection. Technetium

Tc 99m fanolesomab is intended for a single intravenous administration through an intravenous access that has been demonstrated to be patent, e.g., butterfly, running IV line, or equivalent injection system to assure that no dose infiltration occurs. Following administration, flush the injection line with an appropriate volume of saline to assure administration of the total dose.

Dose adjustment has not been established in patients with renal insufficiency, in geriatric patients or in pediatric patients under 5 years of age.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The subgroup analysis by gender did not demonstrate difference in safety profiles or efficacy outcome.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Patients enrolled in the clinical studies ranged in age from 5 years to 91 years, with an average age of 38 years. Twenty-nine of 523 patients (5.5%) were between 5 and 11 years old, 32 (6.1%) were between 12 and 16 years old, 398 (76.1%) were between 17 and 64 years, and 64 (12.2%) were 65 or older. Two hundred seventy-nine patients (279; 53.3%) were female and 244 (46.7%) were male. There were 319 (61.0%) whites, 49 (9.4%) blacks, 98 (18.7%) Hispanics, and 24 (4.6%) "other".

No safety or efficacy difference by age, race or ethnicity were identified.

C. Evaluation of Pediatric Program

The were a total of 66 pediatric patients in the program. Sixteen (4%) patients were between 5 years and 9 years old, 50 (11%) were between 10 years and 17 years. There was no information on safety or efficacy in children less than 5 years of age. There was no difference in safety or efficacy by age, race or ethnicity were identified.

Because the number of patients was to important differences in safety and efficacy cannot be excluded.

D. Comments on Data Available or Needed in Other Populations

There were 9 patients with renal impairment and 3 patients with hepatic impairment who were exposed to Technetium Tc 99m fanolesomab. No data in use of Technetium Tc

99m fanolesomab in pregnancy are available. It is not known whether this drug is excreted in human milk and the product has not been studied in nursing mothers.

X. Conclusions and Recommendations

A. Conclusions

The data for efficacy was obtained from a single-arm study that enrolled 203 patients demonstrated that Technetium Tc 99m fanolesomab has a sensitivity of 75%, a specificity of 93% and an accuracy of 88% to diagnose patients with equivocal symptoms and signs of appendicitis. The positive predictive value and negative predictive value were 82% and 90%, respectively.

In general, the adverse event profile and activity outcome were similar in all of patient subgroups examined. It was demonstrated that following administration of the product some patients develop transient neutropenia. The diagnostic performance of the product is related to accumulation of PMNs in the inflamed appendix, therefore the performance of the product in patients with low or high PMNs may differ.

Overall, the studies reviewed indicate that Tc 99m fanolesomab is safe for use in patients 5 –96 years of age to diagnose appendicitis in patients presenting with atypical signs and symptoms. In general, the adverse event profile and activity outcome were similar in all subcategory of patient groups.

B. Recommendations

Based on the review of the data submitted in BLA 103928, it is recommended that the application for Technetium Tc 99m Fanolesomab (Technetium Tc 99m fanolesomab) be approved.

The performance of the product in patients with abnormal neutrophil count (patients with neutropenia) is not known. In addition the HAMA assay validation was inadequate.

We recommend the following as post marketing commitments to the sponsor:

1. Evaluate the clinical performance and safety of Technetium (99m Tc) - Fanolesomab in patients with abnormal polymorphonuclear leukocyte (PMN) counts who have equivocal signs and symptoms of appendicitis.

2. Develop appropriate validated, quantitative immunogenicity assay for the detection of an immune response (binding antibodies) to Technetium (99m Tc) Fanolesomab and asses the incidence of antibody formation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

MEMORANDUM

DATE: September 20, 2000

FROM: Lydia O. Martynec, M.D.
Medical Officer/, Oncology Branch Division of Clinical Trial Design and Analysis (DCTDA)

SUBJECT: Review of the BLA submission 99-1407
Palatin, Inc.
^{99m}Tc-Labeled anti-CD-15 IgM antibody (LeuTech)

THROUGH: Karen Weiss, M.D., Director of the Division of Clinical Trial Design and Analysis (DCTDA)

William Schwieterman, M.D., Branch Chief, Infectious Diseases and Immunology Branch, Division of Clinical Trial Design and Analysis (DCTDA)

TO: File

BLA 99-1407

Sponsor: Palatin, Inc.

Product: Technetium 99^m anti-CD-15 IgM antibody (LeuTech)

Clinical Reviewer : Robert Lindblad

Nuclear Medicine Reviewer : Lydia O. Martynec

Submission Date: November 22, 1999

Material Reviewed: 12 volumes and an imaging database submitted on CD-ROM.

Purpose of Review:

The main focus of this review is to verify the assessment of the scans by the blinded readers, to assess the quality of the provided images for the proposed indication and to review the dosimetry data.

Background :

The data was collected under IND 7358 and consisted of two studies as described below:

Protocol 97-003

This was the Phase 2 efficacy and safety study that provided supporting efficacy data for Tc-99^m LeuTech™product indication.

Protocol 98-004

Title: An Open Label, Multi-Center Clinical Study to Evaluate the Efficacy and Safety of Technetium 99^m LeuTech ™ Scintigraphy for the Detection of Appendicitis in Patients with Equivocal Signs and Symptoms

Study 98-004 was the pivotal, Phase 3 efficacy and safety study for Technetium 99m-Leutech™. The imaging database that was submitted to the blinded reviewers and as part of the BLA was conducted under this protocol.

Dosing:

10-20 mCi: Tc99^m-LeuTech™ (75-125 μg antibody)

Pediatric Dose:

The dose was scaled downward in patients less than 18 years of age based upon the following formula:

0.21 mCi/kg of body weight up to a maximal dose of 20 mCi.

Image Acquisition:

Imaging was performed using a large field of view camera (LFOV) with a low energy, parallel hole, high resolution collimator and photopeaked at 140keV.

The imaging protocol was collected over an approximate 90 minute duration of time and consisted of two phases of image collection: a dynamic and static image phase.

Dynamic image acquisition over the lower abdomen was performed from the time of $Tc99^{m}$-LeuTech™ injection until 10 sequential four minute frames were collected.

Following the dynamic image acquisition, the patient ambulated for approximately 10- 15 minutes and voided.

At this point static planar images were obtained consisting of the following views: supine anterior, posterior, right anterior oblique, left posterior oblique planar images and a standing anterior image of the lower abdomen.

A total of one million counts was collected for the anterior supine image. All remaining images were collected for the same duration of time as the anterior supine image.

Additional images such as SPECT images and delayed planar images were acquired at the discretion of the investigator.

Patients imaged for less than 30 minutes were considered unevaluable for the efficacy analysis.

A total of fifteen patients at selected sites had conjugate anterior/posterior whole body imaging performed.

Imaging data was collected in digital format and recorded on hard copy film. All images were labeled with the site number, patient number and image time.

Image Evaluation:

Investigator Image Evaluation :

The Tc99^{m}-LeuTech^{TM} images were evaluated by the individual site investigators and all information was recorded on the Case Report Form. Images that were technically readable were evaluated as positive (abnormal area of uptake) or negative (no abnormal area of uptake).

In the case of a positive image interpretation the investigator was to note the following:

Location: Appendicitis Zone (outlined on the diagram in the Case Report Form)

Uptake Pattern: Focal
Multifocal
Linear
Diffuse
Other

Intensity of Abnormal Uptake: Low
Moderate
High

The investigator was to note the time the scan first became positive, whether or not the area of abnormal uptake was present during the entire imaging sequence and whether or not there was a positional change in the area of abnormal uptake.

Following the recording of all of the above information, the investigator was to note a "LeuTech diagnosis" of " negative" (no infection) or "positive" (acute appendicitis or other infection).

Images from the first two patients at each site except the lead site (Site A) were considered training cases for the individual site investigators. The images were forwarded to the lead investigator (Samuel Kipper, M.D.) who was to review the images and image interpretations with the site investigators.

Blinded Reader Imaging Protocol

The blinded read protocol submitted to the original BLA lacked a comprehensive description in the Blinded Read Methodology Report regarding the input of data that was presented from the sponsor to the independent contractor, (b) (4) The sponsor was asked to provide this information during the review of the BLA.

The imaging database was evaluated by three independent blinded reviewers, none of whom participated in the Phase 3 trial.

The blinded readers were the following:

(b) (4)

(b) (4) was the blinded reader for both the Phase 2 (Protocol 98-003) and Phase 3 trial (Protocol 98-004).

The initial blinded reader protocol called for a total of four blinded read sessions. In each session data from approximately fifty patients was to be evaluated in a randomized fashion by each of the blinded reviewers. The reviewers underwent a training (discussed above) prior to the first blinded read session. The blinded readers were provided with the criteria for equivocal presentation of appendicitis as defined by the protocol and with pertinent patient demographic information. (sex, age, height, weight). They were not provided with individual patient profiles or outcomes. Each image set was assigned a random code number that determined the order in which the image sets were presented to the readers. The image sets were presented to the three readers in a standard format on computer monitors, with only the randomization code number as identification. Each reader independently viewed a side by side display of images and an electronic Case Report Form.

The image sets were evaluated by the blinded readers using the same criteria as specified for the on -site reader.

All LeuTech blinded reads were developed and conducted by an independent contractor (b) (4) using their software and computer workstations. (b) (4) personnel set up the equipment, managed and monitored the image reading sessions and performed the data collection, quality assurance and data management.

The Phase 3 reads were conducted at the office of (b) (4) California.

(b) (4) received and evaluated hard copy and digital image sets of all 203 patients enrolled from the 10 participating study sites.

Deviations from Blinded Read Study Protocol:

1. Five blinded read sessions were conducted instead of four.

2. The first blinded read session was scheduled to accommodate Dr. Kipper who trained the blinded readers immediately prior to the blinded read session. Only 20 image sets were included in Session 1. The remaining image sets were divided to maintain 45-48 image sets per each reading session.

Training of Blinded Readers:

The blinded readers participated in a single training session conducted by Dr. Samuel Kipper who was the lead investigator in the Phase 2 and Phase 3 trials. The training session was conducted immediately prior to the first blinded read session held in November 1998. The sponsor states that the training session was identical to the training session presented to the Phase 3 site investigators participating in the pivotal trial.

The training program consisted of the following elements:

1. a review on the use of Indium labeled white blood cell imaging in acute appendicitis

2. a review of the use of Tc HMPAO labeled white blood cell imaging in acute appendicitis

3. a review of the Phase 2 study with the presentation of 7 cases

4. practice blinded readings of 15 image cases from the Phase 2 study by each reader (discussed below)

5. following the completion of the practice blinded reads a joint review of the 15 cases to include each reader and Dr. Kipper was conducted

The 15 image cases from the Phase 2 study that were used to train the Phase 3 investigators and blinded readers were preceded by the following components:

a review of image acquisition parameters
the normal biodistribution of the LeuTech antibody
techniques of image interpretation (e.g., review images in temporal sequence, adjust contrast and brightness of images, review dynamic images as an endless loop cine, etc)
LeuTech Urinary Artifacts (activity that is excreted in the urine creates artifacts in the bladder,ureters and kidneys and resolution of the above problems)
LeuTech Bone Artifacts (asymmetric sacroiliac joint can simulate an appendicitis, an iliac crest may simulate a lateral appendicitis)
Significance of LeuTech intestinal activity was discussed (e.g., LeuTech is not excreted in the bowel, bowel activity indicates pathology)

The readers were instructed to interpret images as follows:

Read for highest sensitivity and negative predictive value
Read scans with the mindset of being afraid to miss the diagnosis of appendicitis
Search carefully for appendicitis
Do not give equivocal readings

The readers were provided with scan interpretation criteria for appendicitis. This included the potential location of the appendix on the scan, patterns of uptake that could present as appendicitis, timing of a positive scan and positional changes. Readers were also presented with unusual patterns and location of radiotracer uptake.

The readers were instructed that if abnormal uptake is found outside the appendicitis zone the scan was to be read as negative for appendicitis. The interpretation for a positive scan regarding the uptake pattern, location of abnormal site of uptake and intensity of uptake in the instructions that were provided to the readers conformed to the Case Report Form of the Phase 3 protocol.

The training manual was not submitted to the original BLA but was submitted at a later data at our request. The training manual contained 8 image sets consisting of the following: negative cases (2), positive for appendicitis (5 cases (1/5 perforated appendicitis, 1/5 retrocecal appendicitis) and 1case of colitis. Each image set consisted of hard copy dynamic and static images with a brief description of the patient's presenting signs and symptoms and final outcome. In relevant cases there were arrows on the images provided that pointed to the area of abnormality.

The 15 image sets that were presented to the participating Phase 3 investigators and blinded readers are not contained in the training manual. The sponsor stated that the practice blinded reads of the 15 cases that were taken by each trainee individually were recorded on the a page identical to the questions and format to the electronic Case Report Form used by the blinded readers in the blinded read session.

The results were hand tabulated and performance characteristics of individual accuracy, sensitivity and specificity for each blinded reader was calculated. The individual performance of each blinded reader was discussed with the trainee. These results have not been submitted to the BLA.

Image Review:

The pivotal trial enrolled 203 patients from 10 participating study sites. The independent contractor [redacted] (b) (4) collected the image sets directly from each site.

Of the 203 patients enrolled and imaged in the trial, 200 patients had a digital image data set. The three patients (B-06, J-06 and J-10) that did not have digital data available had their original films scanned into the image database. 196 patients had hard copy films performed. [redacted] (b) (4) translated the vendor specific formats to a standardized common format for the blinded read review and attached a random code number to each image set.

[redacted] (b) (4) was also responsible for the following functions:

- Blind Coding the Image Data to mask all drug, patient and site information
- Preparing the Images for the Image Display for the Blinded Readers
- Design of the Electronic Case Report Form to be used by the Blinded Readers
- Providing the Computer Hardware and Personnel to Conduct the Blinded Reads
- Conducting and Monitoring the Blinded Reads
- Submitting the Complete and Locked Blinded Read Database to the Statistical Group for Analysis

The imaging database shown to the blinded readers was submitted to the BLA on CD-Rom for PC Windows NT viewing by the independent contractor [redacted] (b) (4) [redacted] (b) (4)

The image database contains 203 image sets presented according to site and patient number.

All image sets in the database were assessed by the reviewer.

The nuclear medicine reviewer's assessment of the image database consisted of the following:

Adherence to protocol
Completeness of the Dynamic Image DataSet (10 sequential 4-minute images)
Completeness of the Planar Image DataSet (Supine Anterior, Posterior, RAO, LAO, Standing Anterior)
Technical Quality of the Study Based on the Clarity of the Dynamic and Static Images
Diagnosis of Positive or Negative
Time of Positive Images Following Injection

The quality of the planar images was judged by the usefulness of the gray scale to improve contrast in the abdomino-pelvic area, prominence of the urinary bladder, timing of the images and absence of site or patient identification. The overall image quality was judged to be good only if all static images were good.

Image quality was good according to the criteria discussed above. The following comments pertain to the image quality:

- All 203 image sets were missing the timepoint label
- The Image database allowed the reader to manipulate the image contrast and color display with ease
- All image sets had patient information (name, site name) redacted
- The Dynamic Image Data Set was Complete (10 or more sequential images) in 196/203 patients. The following patients did not have a complete dynamic phase image set: Patient A-002(8 sequential images), Patient # A-0029 (8 sequential images), Patient # E-009 (5 sequential images), Patient # H-001(8 sequential images), Patient # H-010 (8 sequential images), Patient # H-014(8 sequential images) and Patient # J-010 (9 sequential images)
- The Static Planar Image Data Set was complete (5 static views) in 164/ 203 patients. The missing views in the majority of cases was the standing anterior view (171/203), followed by the posterior view (186/203), Left anterior oblique view(195/203), right anterior oblique view (197/203) and anterior view (198/203).
- 1/203 images were technically unevaluable; Patient # B-006 had films scanned in (non-digital data) ; the remaining image sets were technically evaluable

Image Interpretation:

The biodistribution of Technetium Tc-99m Anti-CD 15 Antibody radiopharmaceutical is seen in the blood pool, reticuloendothelial system (liver, spleen, bone marrow) and urinary excretion organs (kidneys, bladder)). Blood pool activity within the uterus may also be visualized. Clearance of the Technetium Tc-99m Anti-CD 15 Antibody via the kidney and urinary bladder was identified. No intestinal or biliary excretion was seen.

A positive image finding is characterized by an asymmetric uptake in the lower abdominal quadrant that typically remains constant or increases in intensity with time.

Table 1 depicts the proportion of patients with true positive images read as positive for each blinded reader based on a total of 59 patients with true surgical appendicitis.

Table 1

IMAGE INTERPRETATION	PROPORTION OF TRUE POSITIVE PATIENTS WITH IMAGES READ AS POSITIVE			
	0 to 30 min. N (%)*	0 to 60 min. N (%)*	0 to 90 min. N (%)*	**Total** n=59
Blinded Reader 1	38/48 (79%)	46/48 (96%)	48/48 (100%)	48/59 (81%)
Blinded Reader 2	32/39 (82%)	39/39 (100%)	39/39 (100%)	39/59 (66%)
Blinded Reader 3	30/45 (67%)	44/45 (98%)	45/45 (100%)	45/59 (76%)
Average	76%	98%	100%	75%

N(%) * In each case N denotes the # of scans read as positive at each time point based on the total number of true positives for each reader; Percentages are cumulative over time

In the clinical trial, based on the average of the three blinded reader interpretations, 75% of the 59 true positive cases of appendicitis were identified (range 66%-81%).

Among those with a blinded reader diagnosis of appendicitis, 76% displayed uptake of radiotracer activity in the appendix within 30 minutes following injection and 98% did so by 60 minutes following injection of Technetium Tc-99m Anti-CD 15 Antibody.

Radiation Dosimetry

Based on human data, the absorbed radiation dose to an average human adult (70 kg) from an intravenous injection of the agent is listed in Table 2. The values were calculated using the Standard Medical Internal Radiation Dosimetry (MIRD) method. The exposure estimates were within the expected range for a diagnostic imaging agent labeled with Technetium. The values are listed as rad/mCi and mGy/MBq and assume urinary bladder emptying at 4.8 hours. Radiation absorbed dose estimates for children based on biodistribution studies in adults are given in Table 3.

Table 2. Estimated absorbed radiation dose in adults

Target Organ	rad/mCi	MGy/MBq
Spleen	0.23	0.062
Kidneys	0.19	0.051
Liver	0.18	0.048
Urinary Bladder Wall	0.12	0.032
Heart	0.061	0.017
Gallbladder	0.056	0.015
Upper Large Intestine Wall	0.051	0.014
Adrenal Glands	0.044	0.012
Lungs	0.043	0.012
Thyroid Gland	0.042	0.011
Red Marrow	0.038	0.010
Lower Large Intestine Wall	0.034	0.0091
Bone Surface	0.031	0.0083
Brain	0.0052	0.0014
Testes / Ovaries	0.0039 / 0.019	0.0010 / 0.0052
Total Body	0.019	0.0050

Dose calculations were performed using the standard MIRD method (MIRD Pamphlet No. 1 rev., Soc. Nucl. Med., 1976). Effective dose equivalent was calculated in accordance with ICRP 53 (Ann. ICRP 18, 1-4, 1988) and gave a value of 0.018 mSv/MBq (0.068 rem/mCi).

Table 3. Estimated absorbed radiation dose for a five-year old child

Target Organ	rad/mCi	MGy/MBq
Spleen	0.70	0.19
Kidneys	0.43	0.11
Liver	0.41	0.11
Urinary Bladder Wall	0.27	0.072
Upper Large Intestine Wall	0.21	0.056
Thyroid Gland	0.19	0.052
Lower Large Intestine Wall	0.16	0.042
Heart	0.15	0.041
Gallbladder	0.13	0.036
Red Marrow	0.11	0.030
Lungs	0.11	0.028
Adrenal Glands	0.095	0.026
Bone Surface	0.085	0.023
Testes / Ovaries	0.019 / 0.059	0.0052 / 0.016
Brain	0.0075	0.0020
Total Body	0.049	0.013

Dose calculations were performed using the standard MIRD method based upon biodistribution studies conducted in adults. Effective dose equivalent was calculated in accordance with ICRP 53 and gave a value of 0.047 mSv/MBq (0.17 rem/mCi).

The dosimetry data was submitted to an independent contractor (b) (4) (b) (4) His conclusion was that the study design, the kinetic modeling and the dosimetry methods, were appropriate and correct and that the dosimetry data based on the raw activity reviewed by him accurately reflect the actual dosimetry of Tc99^{m}-LeuTech™ product.

Conclusions:

In conclusion, review of the image data set demonstrate it is adequate to support the efficacy claim of the Tc99^{m}-LeuTech^{TM} product.

In future Phase 4 studies the sponsor should be encouraged to perform dosimetry studies in the pediatric population.

Lydia O. Martynec
9/20/00

Lydia O. Martynec,M.D.
Medical Reviewer
CBER/DCTDA/Oncology Branch

Bill Schwieterman,M.D.
Branch Chief
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June 3, 2004

I concur with Dr. Martynec's assessment.

Louis Mazzella MD PhD
Team Leader
Immunology and Infectious Diseases
DTB/IMP/ODE6

BLA # 99-1407

Sponsor:	**Palatin**
Product:	**Sodium Pertechnetate Tc 99m labeled Murine Monoclonal Antibody (LeuTech®)**
Submission Date:	**11/26/99**
Clinical Reviewer:	**Robert Lindblad, M.D.** 9-1-00

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Section I
A. Introduction

Purpose: This document presents data from clinical studies of LeuTech as submitted in the BLA application from Palatin and an analysis of these data.

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 accumulation of PMNLs has occurred. 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. Two or more inflammatory conditions located at the same site would inherently be difficult to differentiate.

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, sites of inflammation, specifically the appendix, could potentially be identified.

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 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	24 patients
Physician Sponsored IND (not under Palatin IND):			
Open label to evaluate HAMA -	completed	Phase 1	30 patients
Infectious process	ongoing -	Phase1/2	69 patients
Infectious process	completed (German) -	Phase 1	17 patients

C. Medical Imaging Device Advisory Committee

A medical Imaging Device Advisory Committee (MIDAC) was convened July 10, 2000 to comment on the data as presented by Palatin and the Agency. Questions were posed to the committee including:

- Entry criteria
- Adequacy of the safety data base
- Clinical utility

A vote as to the adequacy of the data to support the safety and efficacy of the scan was unanimously favorable.

Questions were raised concerning the safety of the scan in neutropenic patients in addition to the need to consider postmarketing studies should the product be approved

Section II – Phase 2

A. Investigational Plan Phase 2

Palatin initially conducted a phase 2 study in a small number of patients. The following is 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)

Reviewer comment: The entry criteria were not as well defined in this phase 2 study as compared to the phase 3 study. These entry criteria will be discussed in more detail with the phase 3 trial.

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.

Reviewer comment: This questionnaire and the modification as outlined provided the foundation for evaluating the clinical utility of this product. This construct of the case report form and the timing and dating of these forms, as defined in the phase 2 study, was used effectively in the phase 3 trial. It is also clearly spelled out that the principal investigator would have the surgeon complete these forms.

6. Performance 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 performance outcome measures:

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

b. Secondary performance 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.

Reviewer comment: In this phase 2 trial performance is principally defined by the sponsor as the agreement between blinded offsite readers and the patient's actual diagnosis as defined above. This relies on the quality of the scan alone without the introduction of biases provided by the onsite readers.

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.

Table 1: Phase 2 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: Phase 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: Phase 2 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.

Table 4: Phase 2 Distribution Of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) And Antibiotics Taken within 24 Hours of Tc 99m LeuTech Injection.

MEDICATION CLASS	NUMBER OF PATIENTS	(%)
NSAIDs	3	5
Antibiotics	5	9

Reviewer comment: Concomitant antibiotic use was somewhat more common in the phase 3 trial as compared to this trial. The role of antibiotic use and the scan results are discussed later in this document.

Table 5: Phase 2 Other Medications Taken Within 24 Hours of Tc 99m LeuTech 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: Phase 2 Distribution of Final Institutional Diagnosis for Appendicitis/No Appendicitis and Infection/No Infection.

	ACUTE APPENDICITIS		NO ACUTE APPENDICITIS	
	N	%	N	%
SITE A	26	53	23	47
SITE B	2	29	5	71
Total	28	50	28	50
	INFECTION		NO INFECTION	
	N	%	N	%
SITE A	29	59	20	41
SITE B	6	86	1	14
Total	35	63	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.

Table 7: Phase 2 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

Reviewer comment: Two cases of PID were noted in this trial. PID was an exclusion criteria in the phase 3 trial. The experience with PID therefore is extremely limited.

C. Primary Performance Results:

1. Blinded Readers Appendicitis

The phase 2 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.

Table 8: Phase 2 Blinded Reader: Tc 99m LeuTech 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

Reviewer comment: This is comparable to the onsite readers in the phase 3 trial, but not the blinded readers. The phase 3 blinded readers had a higher specificity than sensitivity.

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.

Table 9: Phase 2 Measures of Inter-Reader Agreement for Diagnosis of Appendicitis/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 Performance Results

1. Site Investigators: Appendicitis

Of note, the onsite readers did consistently better than the blinded readers, though there was not a dramatic difference between the two. 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. Table 10 shows data for the onsite readers diagnosing appendicitis

Table 10: Phase 2 Site Investigators: Patient-Based Agreement Rate, Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value Of Tc 99m LeuTech Images with Final Institutional Diagnosis, Appendicitis/No Appendicitis.

AGREEMENT RATE	NT	TP+ TN	Agreement Rate (%)	95% Confidence Int.	
				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	N(+)	TP	Sensitivity	95% Confidence Int.	
				LL	UL
SITE A	26	26	100	84	100
SITE B	2	1	50	3	84
Combined	28	27	**96**	80	97
SPECIFICITY	N(-)	TN	Specificity	95% Confidence Int.	
				LL	UL
SITE A	23	19	83	61	92
SITE B	5	3	60	17	85
Combined	28	22	**79**	59	90
POSITIVE PREDICTIVE VALUE	TP + FP	TP	Positive Predictive Value	95% Confidence Int.	
				LL	UL
SITE A	30	26	87	68	94
SITE B	3	1	33	2	77
Combined	33	27	**82**	64	91
NEGATIVE PREDICTIVE VALUE	TN +FN	TN	Negative Predictive Value	95% Confidence Int.	
				LL	UL
SITE A	19	19	100	79	100
SITE B	4	3	75	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 11 describes patients who had surgery, but ultimately were not diagnosed with appendicitis.

Table 11: Phase 2 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 12 describes the clinical management and intended disposition of patients based on the surgeon questionnaire, both pre and post LeuTech scanning.

Table 12: Phase 2 Shifts in Management /Disposition

Pre-scan Disposition	N	Post-scan Disposition	N	Patients with Appendicitis #	(%)
Home	6	Home	4	0	0%
		Observation	0	0	0%
		Surgery	2	2	100%
Observation	38	Home	13	0	0%
		Observation	9	3	33%
		Surgery	16	15	96%
Surgery	12	Home	2	0	0%
		Observation	0	0	0%
		Surgery	10	8	80%

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

Table 13: Phase 2 Distribution Of Confidence In Intended Clinical Management Pre- And Post-Tc 99m LeuTech 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 description 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 used a five point scale based on the surgeon's likelihood estimate of appendicitis as depicted in table 16. Both evaluations showed a positive shift in a surgeon's confidence in the diagnosis of appendicitis.

b) Second half of study

Table 14 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 14: Phase 2 Distribution of Estimates of Likelihood of Appendicitis Pre- and Post-Tc 99m LeuTech 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.

F. Safety:

Table 15 shows the adverse events associated with the administration of LeuTech.

Table 15: Phase 2 Adverse Events Following Administration of Tc 99m LeuTech

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.

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%

Reviewer comment: No significant adverse events were noted in the phase 2 study. Both on-site and off-site readers demonstrated favorably high levels of sensitivity, but lower specificity. There is noted a relatively high incidence (50%) of appendicitis in the population studied. These phase 2 data support the positive performance of the LeuTech scan.

Section III – Phase 3

A. Investigational Plan-Phase 3

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 McBurney'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 $10,500/mm^3$)

Reviewer comment: These entry criteria are more specific than the entry criteria in the phase 2 trial. In an attempt to define a patient population that is more atypical than that in the phase 2 trial, they were successful in reducing the incidence of appendicitis from 50% in phase 2 to 30% in the phase 3 trial. However, besides right lower quadrant pain, a subject could have as few as one of the above 9 criteria, or all 9 of them and qualify for the study. In patients that had only one positive atypical finding the incidence of appendicitis was 71%. No Patient with 7, 8 or 9 atypical findings had appendicitis. This will be presented in more detail later.

b. 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 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.

Reviewer comment: PID is an important exclusion criterion. It was excluded based on a pelvic exam suggestive of PID during the initial evaluation for entry in the study. As both appendicitis and PID involve infection/inflammation in the same area, there could be a significant overlap in scan results. This issue was not addressed in this study and remains to be resolved.

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 had 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.

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 completed 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

assumed that the Tc 99m LeuTechTm scan was highly sensitive and accurate for the diagnosis of appendicitis. The principal investigator assured that the referring surgeon completed both questionnaires for each patient according to the schedule outlined.

Reviewer comment: The clear timing and dating of these case report forms allowed this reviewer to evaluate the clinical utility of the scan.

The final institutional diagnosis was recorded on the CRF. If a patient underwent surgery, copies of the surgical report and pathology report were 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 obtained. Patients were 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 contacted by telephone to obtain the clinical follow-up. If appropriate, reports of any subsequent hospital and/or physician visits, tests or treatment were obtained and reviewed. In addition, results from additional diagnostic procedures (e.g., ultrasound, spiral or conventional CT) were 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 repeated at two hours following administration of Tc 99m LeuTechTm or immediately prior to surgery or discharge, whichever came first. The following studies were performed:

1) Hematology:

hematocrit
hemoglobin
platelet count
white blood cell (WBC) count
WBC differential
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 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 collected in red-top tubes (no anticoagulant) and allowed to clot. Following centrifugation, serum was separated and aliquots of approximately 1 ml serum were stored frozen ($\leq -20^0$ C) in polypropylene cryogenic tubes. One of the pair of duplicate specimens was kept at the site and the other was shipped on dry ice to the laboratory where the HAMA analyses were performed.

Each sample was 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.

B. Results Phase 3

1. Demographics

The demographics of patients enrolled in the phase 3 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 16-18.

Table 16: Phase 3 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 10 1 ^{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 17: Phase 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 18: Phase 3 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 is displayed in table 19. This is followed by the incidence of appendicitis at the various sites in table 20.

Table 19: Phase 3 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 20: Phase 3 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)**

Reviewer comment: There is a wide variation in the distribution of patients at the 10 sites ranging from 19% of down to 2% of patients at a given site. There was also a wide variation in the incidence of appendicitis ranging from 0% to 75%. This reflects the broad entrance criteria and the room to include a wide range of patients with a varying likelihood of appendicitis.

b. Distribution of Surgical patients

Table 21 represents the patients by site, which went to surgery.

Table 21: Phase 3 Distribution of Patients who Underwent Surgery.

SITE	#SURGERY PATIENTS	# ACUTE APPENDICITIS	OTHER FINDINGS	# NEGATIVE PATIENTS
A	13	10	1 ruptured bladder (A- 15) 1 periappendicitis (A-21)	1
B	5	3	1 retrocecal abscess (B-12)	1
C	2	0	1 periappendicitis (C-02) 1 Crohn's disease with impending obstruction (C-03)	0
D	9[1]	8	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. Non-Evaluable Patients

Table 22 represents patients that were non-evaluable for the phase III study. This represent only ~1% of the study patients.

Table 22: Phase 3 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.

2. Defining an Atypical Appendicitis Patient Population

a. Introduction

This product was studied with the intent to aid in the diagnosis of those patients with atypical signs or symptoms of appendicitis. As alluded to earlier, patients only needed one atypical finding to qualify for this study, or could have all nine atypical findings and still qualify for the study. This produced a range of incidence of appendicitis at the study sites from 0 – 75%. Though the average incidence of appendicitis for the entire study patient population was 30%, a proportion of those patients fell at the two extremes; those that clearly had appendicitis, and those that clearly did not have appendicitis. The following section addresses these concerns and attempts to define an atypical appendicitis patient population by defining and excluding those extremes. This will be done by; 1) looking at the entry criteria, 2) the surgeon's pre-scan disposition plan, and 3) the surgeon's pre-scan likelihood estimates.

b. Entry Criteria

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 23 depicts the distribution of the major signs and symptoms as derived from the entrance criteria.

Table 23: Phase 3 Distribution of Major Signs and Symptoms

	PATIENTS	
	N[1]	%
Atypical history and/or symptoms	148	73%
Atypical physical examination	138	68%
Temperature 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

These entry criteria do very little to define an atypical patient population individually. The typical case of appendicitis has a temperature less than 101^0F and this is considered an atypical finding. These findings also vary over time, so that a patient early in the course of appendicitis will have different signs and symptoms than a patient late in the course.

In patients who had a final institutional diagnosis of appendicitis (N=59), of the four major criteria, it was uncommon to have a normal WBC and very common to have a temperature less than 101^0F.

Table 24: Phase 3 All Patients with Appendicitis N=59

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

There was no clear correlation of any individual sign or symptom and the likelihood of appendicitis. However it did make a difference how many of those signs and symptoms a given patient had positive. The more atypical findings present, the less likely that a patient had appendicitis. This is represented in table 25.

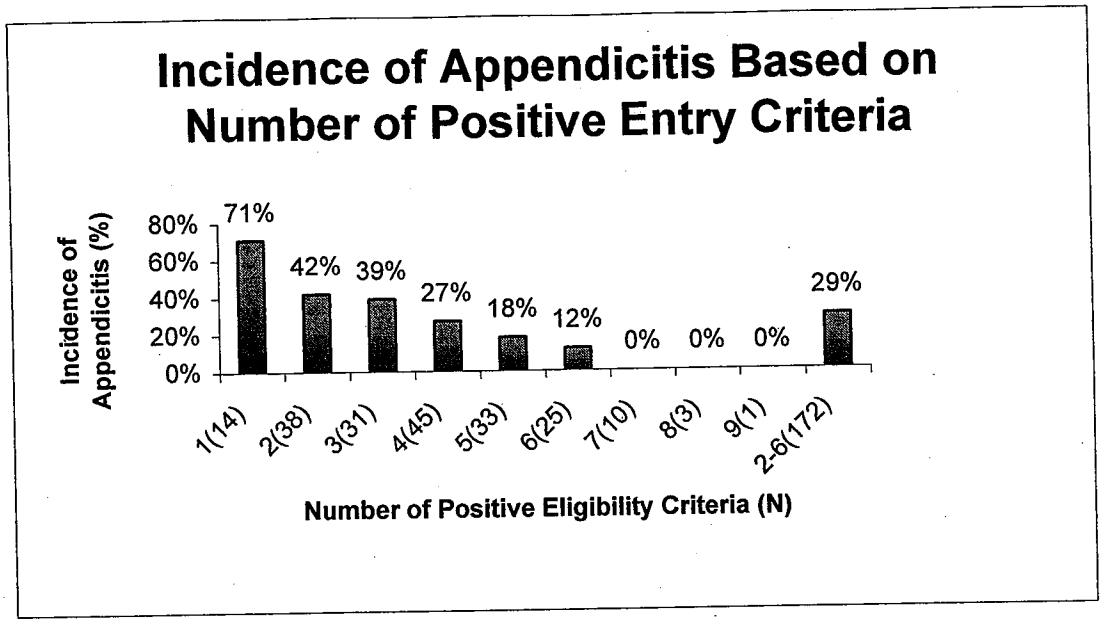
Table 25: Phase 3 Incidence of Appendicitis versus the Number of Positive Major Entry Criteria

# of Positive Major Entry Criteria	N	Incidence
1	16	63%
2	53	49%
3	69	26%
4	62	8%
Total	200	

For the four major criteria, a greater number of atypical findings translated into a decreased chance of having appendicitis. Looking at all nine criteria, as the study was designed, further demonstrates this point.

Table 26: Phase 3 Incidence of Appendicitis versus the Number of Positive Entry Criteria

# of Positive Entry Criteria	N	Incidence
1	14	71%
2	38	42%
3	31	39%
4	45	27%
5	33	18%
6	25	12%
7	10	0%
8	3	0%
9	1	0%
2-6	172	29%
Total	200	



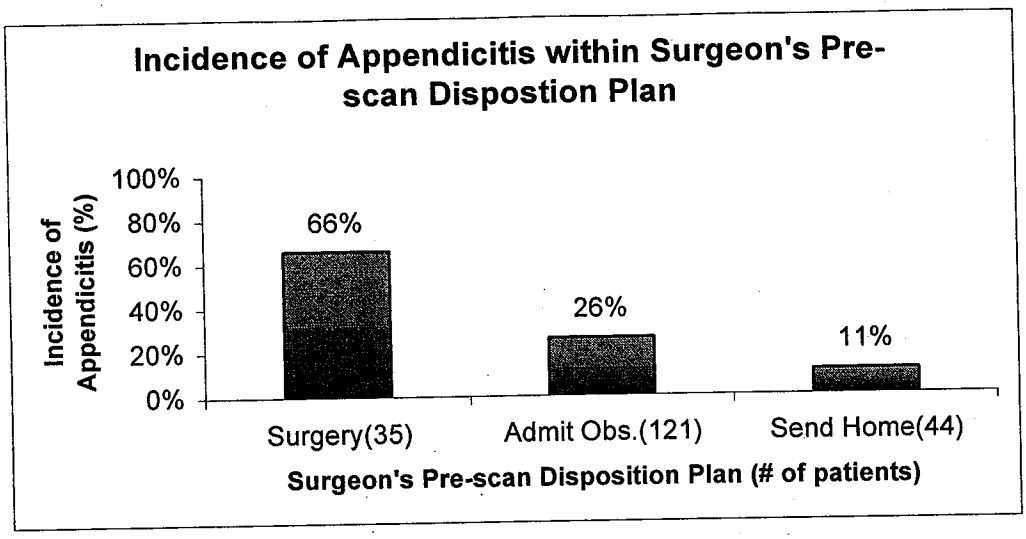
Those patients with only one atypical finding and otherwise having classic appendicitis had over a 70% incidence of the disease. In the group with 7, 8, or all 9 atypical findings, there were no cases of appendicitis. Patients with 2-6 positive atypical findings had an average 29% incidence of appendicitis, as did the overall group. This group of 2-6 atypical findings eliminates the two extremes, both those with a high incidence and those with a low incidence of appendicitis.
This eliminates 28 of the 200 evaluable patients leaving a subgroup of 172 patients.

c. Pre-scan Disposition Plan

Another target group of this study is the patient population that on the pre-scan disposition plan, the surgeons felt they needed to admit for observation. This choice was made based on history, physical exam and laboratory evaluation and prior to obtaining any imaging studies. This subgroup has the highest uncertainty as far as definitive patient management. As such, it represents the group for the greatest utility for a diagnostic agent. The number of patients in this subcategory is listed below.

Table 27: Phase 3 Incidence of Appendicitis versus the Pre-scan Disposition Plan

Pre-scan Disposition Plan		
	N	Incidence of Appendicitis(%)
Send Home	44	11%
Admit for Observation	121	26%
Surgery	35	66%

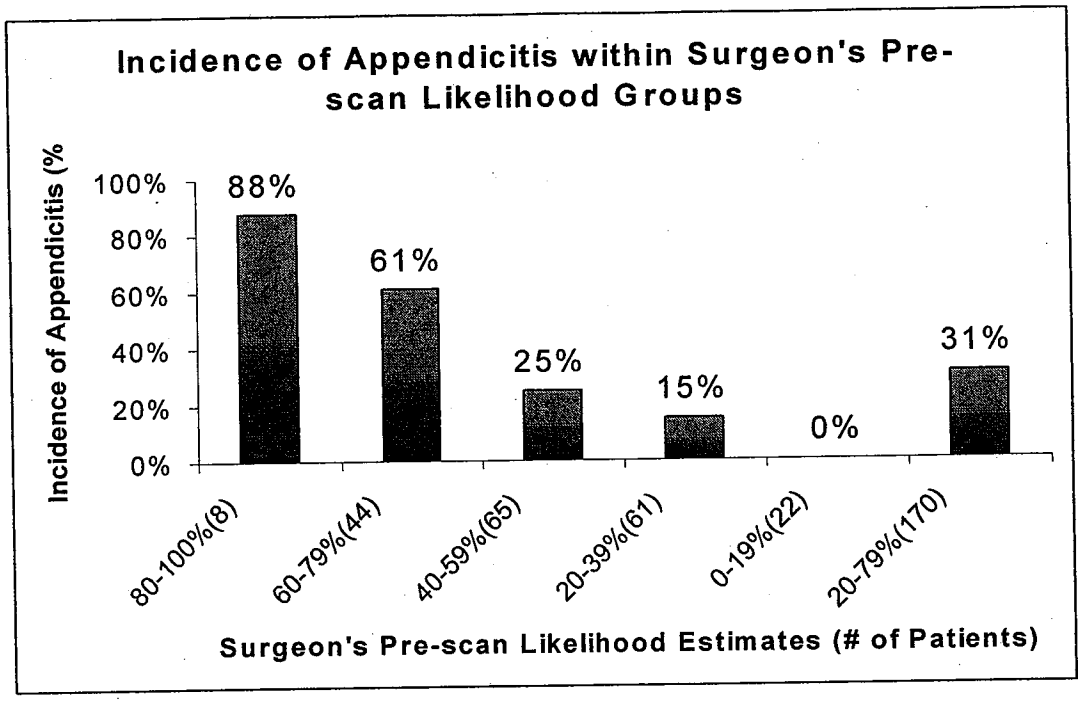


d. Surgeon's Pre-scan Likelihood Estimates

In the management questionnaire, surgeons were asked to estimate the likelihood of appendicitis. As with the disposition determination, this was based on clinical and laboratory assessment and prior to diagnostic procedures. The likelihood estimate was a 5-point scale with the low end being "almost definitely not appendicitis", and the high end being "almost definitely appendicitis." The tables and charts below explore these groups.

Table 28: Phase 3 Incidence of Appendicitis versus the Surgeon's Pre-scan Likelihood Estimate

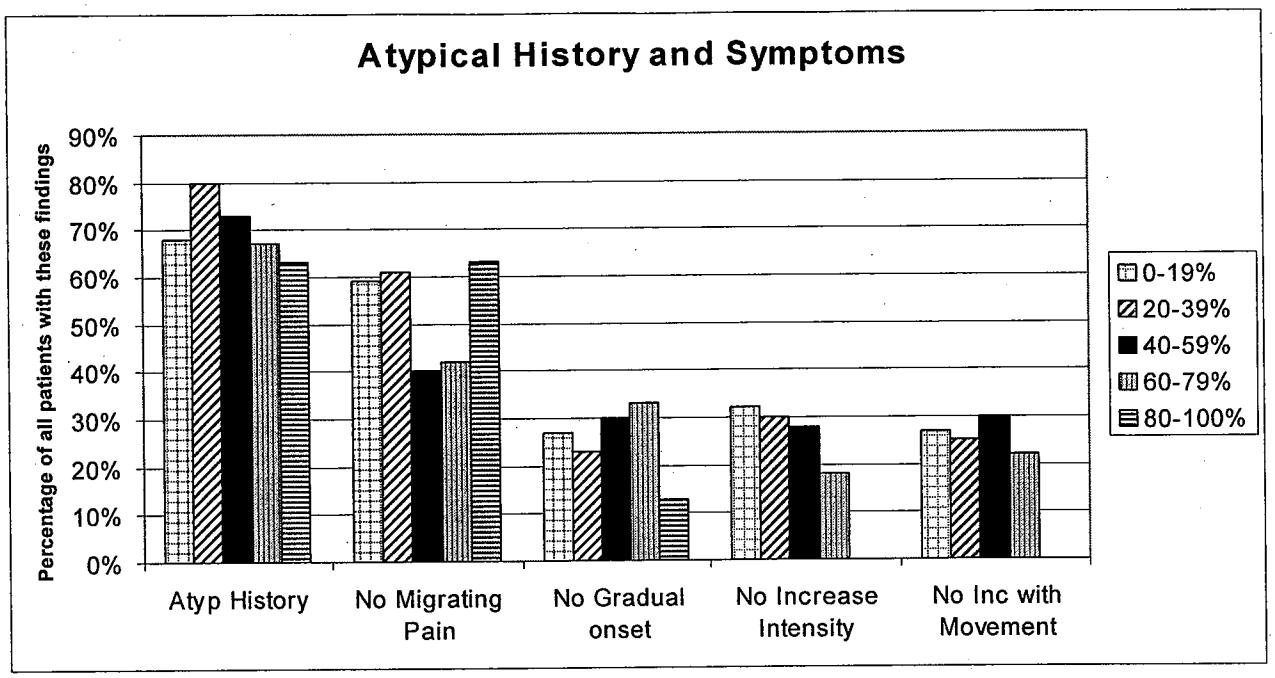
surgeon's pre-scan likelihood estimate	N	Incidence
80-100%(8)	8	88%
60-79%(44)	44	61%
40-59%(65)	65	25%
20-39%(61)	61	15%
0-19%(22)	22	0%
20-79%(170)	170	31%

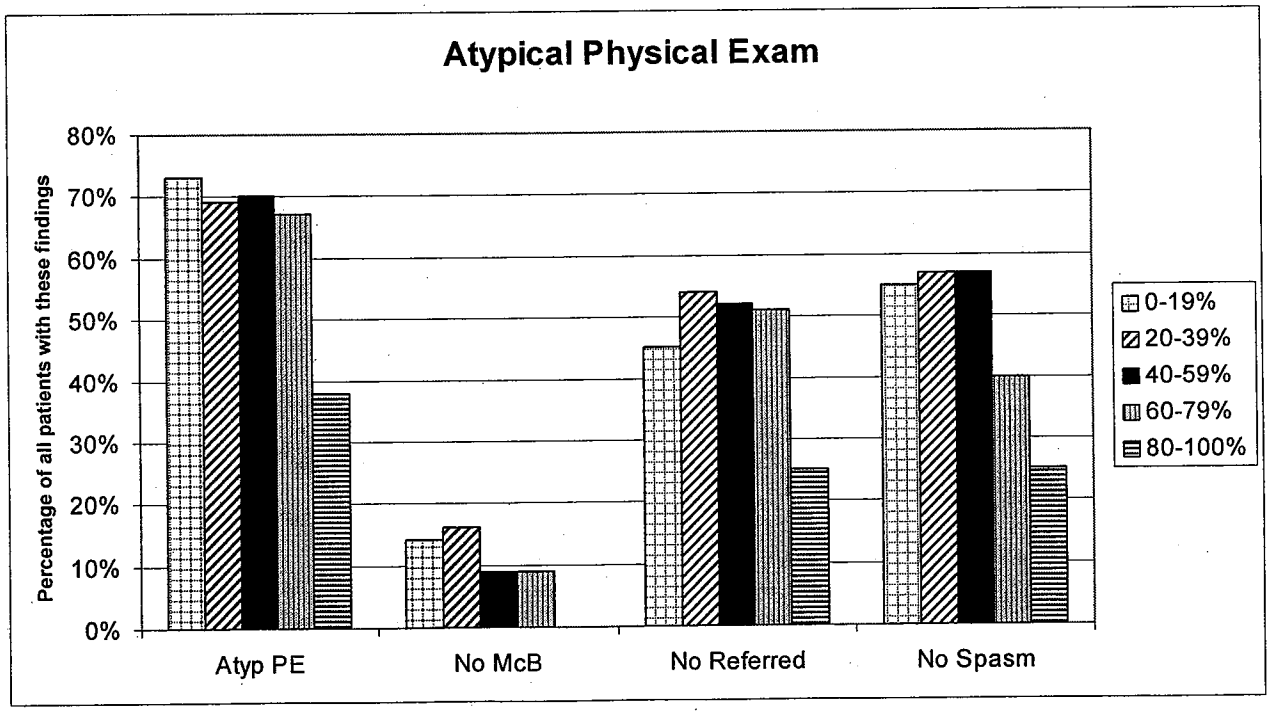


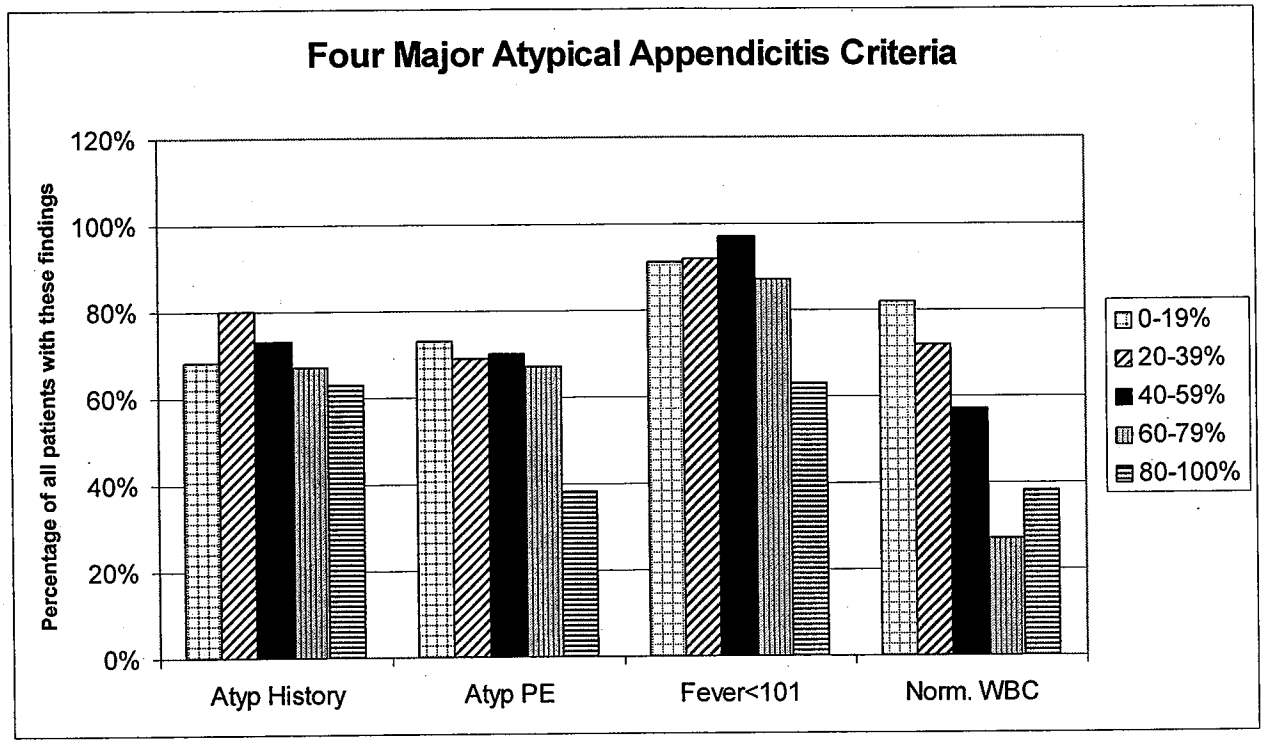
The surgeon's pre-scan likelihood estimates correlated fairly well with the true incidence of appendicitis within this study population. Using this pre-scan likelihood estimate, the individual entry criteria were examined in order to look for specific signs and symptoms that correlated with the incidence of appendicitis. As the pre-scan likelihood estimate increased from 0-19% to 80-100%, the number of patients with a given atypical finding should decrease. These data are presented below.

Table 28: Phase 3 Incidence of Appendicitis versus the Surgeon's Pre-scan Likelihood Estimate and Individual Entry Criteria

% 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%


Atypical History and Symptoms
Percentage of all patients with these findings
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Atyp History
No Migrating Pain
No Gradual onset
No Increase Intensity
No Inc with Movement
0-19%
20-39%
40-59%
60-79%
80-100%


Atypical Physical Exam
Percentage of all patients with these findings
80%
70%
60%
50%
40%
30%
20%
10%
0%
Atyp PE
No McB
No Referred
No Spasm
0-19%
20-39%
40-59%
60-79%
80-100%



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 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 the WBC.

e. Summary

Creating a study design that selects an atypical appendicitis patient population is truly difficult. The criteria used in this study are reasonable. An additional criterion that should be considered for future studies is anorexia. No single criterion, other than perhaps the WBC count, correlated well with the surgeon's pre-scan likelihood estimates and the underlying incidence of appendicitis. Selecting patients based on just one positive criterion or as many as nine allowed too broad a range of patients. Some of these patients were classic appendicitis cases, and others were highly unlikely to have appendicitis. Despite these broad parameters, the majority of the time, the investigators selected a patient population that more closely resembled an atypical appendicitis population. This is reflected in the 172 patients with 2-6 positive entry criteria, patients whose initial disposition plan was admit for observation (N=121) and those patients with a 20-79% pre-scan likelihood of appendicitis (N=170).

C. Performance

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.

Reviewer comment: 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 29 shows the on-site investigators performance outcome measures. These include sensitivity, specificity, accuracy, PPV and NPV.

Table 29: Phase 3 Site Investigator Performance

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 performance 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 30: Phase 3 Blinded Read Performance

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

Reviewer comment: Scans read by the blinded readers had much better specificity vs. sensitivity and a better NPV. The blinded readers in this phase 3 trial also had a better specificity than any of the other studies as well.

c. Intent to Treat

Table 31 shows the intent to treat analysis.

Table 31: Phase 3 Intent to Treat Analysis

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.

Reviewer comment; This phase 3 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 32: Phase 3 Comparison of ITT and Evaluable Patients

	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

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 33 shows the blind reader concordance rate.

Table 33: Phase 3 Blinded Reader Concordance

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

Table 34: Phase 3 Likelihood Ratios

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. These subgroups are broken down into the atypical appendicitis patient population subgroups:

- Entry Criteria
- Pre-scan disposition plan
- Pre-scan likelihood estimate

This will be followed by other patient populations including:

- Patients based on their WBC counts
- Women between 14-35y
- Pediatric: 5-9y and 10-17y
- Geriatric >65y
- "Other infections"
- Patients who also had CT scans performed

The sponsor investigated other sub-populations, which will be briefly discussed. These include populations based on:

- Age group
- Gender
- Race
- Weight (BMI)
- Enrollment order

1. Entry Criteria

As discussed previously, the entry criteria were broken down into the number of positive criteria for an individual patient, and the incidence of appendicitis. The performance of the scan in these groups and the 2-6 positive entry criteria is shown below. This is presented for the aggregate blind read in the evaluable patient population. As was shown earlier, there are only minor differences from the intent to treat and the evaluable groups, and the onsite and blinded readers group.

Table 35: Phase 3 Performance Based on Number of Positive Entry Criteria

# of Positive Entry Criteria	N	TN	TP	FN	FP	Incidence	Sensitivity	Specificity	PPV	NPV
1	14	4	8	2	0	71%	80	100	100	67
2	38	19	9	7	3	42%	56	86	75	73
3	31	19	10	2	0	39%	83	100	100	90
4	45	31	10	2	2	27%	83	94	83	94
5	33	23	4	2	4	18%	82	67	85	50
6	25	22	3	0	0	12%	100	100	100	100
7	10	9	0	0	1	0%	*	90	*	100
8	3	3	0	0	0	0%	*	100	*	100
9	1	1	0	0	0	0%	*	100	*	100
Total	200	131	44	15	10	30%	75	93	82	90
2-6	172	114	36	13	9	29%	73	93	80	90

Table 36: Phase 3 Performance Based on Number of Positive MajorEntry Criteria

# of Positive Major Entry Criteria	N	TN	TP	FN	FP	Incidence	Sensitivity	Specificity	PPV	NPV
1	16	6	8	2	0	63%	80	100	100	75
2	53	24	17	9	3	49%	65	89	85	73
3	69	47	15	3	4	26%	83	92	79	94
4	62	54	4	1	3	8%	80	95	57	98
Total	200	131	44	15	10					

Removing those patients that had only one positive entry criterion or as many as 7, 8, or 9 positive criteria did not alter the performance of the scan significantly.

2. Pre-scan disposition Plan

Another group of patients that reflect an atypical appendicitis population is the group that the pre-scan disposition would be to admit the patient for observation. The performance of the scan in this subgroup is presented below.

Table 37: Phase 3 Performance Based on Pre-scan Disposition Plan

Disposition	N	TN	TP	FN	FP	Incidence	Sensitivity	Specificity	PPV	NPV
Home	44	37	3	2	2	11%	60	95	60	95
Surgery	35	10	20	3	2	66%	87	83	91	77
Observation	121	84	21	10	6	26%	68	93	78	89

The admit for observation group has a slightly lower incidence of appendicitis than the overall population, a lower sensitivity, but the specificity and NPV are maintained.

3. Pre-scan likelihood estimate

The performance of the scan using the surgeon's pre-scan likelihood estimates is displayed below.

Table 38: Phase 3 Performance Based on Surgeon's Pre-scan Likelihood Estimate

Surgeon's pre-scan likelihood estimate	N	TN	TP	FN	FP	Incidence			Sensitivity	Specificity
						TOTAL	If scan + (PPV)	If scan – (100%NPV)		
0-19%	22	22	0	0	0	0%	-	-	-	100%
20-39%	61	51	6	3	1	15%	86%	6%	67%	98%
40-59%	65	43	12	4	6	25%	67%	8%	75%	88%
60-79%	44	14	20	7	3	61%	86%	33%	74%	82%
80-100%	8	1	6	1	0	88%	100%	50%	86%	100%
20-79%	170	108	38	14	10	31%	79%	11%	73%	92%

The performance of the scan in the group with a 20-79% pre-scan likelihood is similar to the overall performance of the scan. Though the numbers are small, the higher the predicted likelihood of appendicitis, the greater the incidence of appendicitis despite a negative scan.
If the scan is negative but there is a high clinical suspicion of appendicitis, the true incidence of appendicitis could be up to 50%.

4. Patients based on WBC counts

The WBC count is of interest for two reasons. First, the WBC count was the entry criteria that most closely correlated with the surgeon's pre-scan likelihood estimate, and as will be shown below, it correlates with the actual incidence of appendicitis. Secondly, this scan tags neutrophils and may therefore be dependent on the number of neutrophils at a given site of inflammation and indirectly on the number of circulating neutrophils.
The performance of the scan is broken down into subcategories of patients with low or elevated WBC counts. This is based on the blind aggregate read.

Table 39: Phase 3 Performance Based on the WBC Count

WBC (/mm3)	N	Incidence	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
4,000 - 7,000	38	11%	32	1	3	2	25	94	33	91
7,000 - 10,000	67	10%	56	5	2	4	71	93	56	97
10,000 - 15,000	57	46%	29	18	8	2	69	94	90	78
15,000 - 20,000	28	54%	11	14	1	2	93	85	88	92
> 20,000	10	70%	3	6	1	0	86	100	100	75

As is shown, the incidence of appendicitis climbs as the WBC count rises. The sensitivity is low with a low WBC but there were only 4 cases of appendicitis. Specificity was well maintained.

5. Women between 14-35y

Women during reproductive years always present a diagnostic challenge when presenting with lower abdominal pain. Within this study it is important to remember that pregnancy and PID were both exclusion criteria. The performance is presented for the aggregate blind read and those women between 14-35y with a surgical pre-scan likelihood of 20-79%.

Table 40: Phase 3 Performance in Women 14 – 35 y

	N	Incidence	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
Women 14-35y 20-79% Likelihood	52	19%	40	8	2	2	80%	95%	80%	95%

6. Pediatric: 5-9y and 10-17y

The pediatric data is presented from pooled phase 2 and phase 3 data. The studies have comparable eligibility criteria and performance determinations based on three blinded readers as has been outlined. Pooling this data allows a greater number of patients to be

assessed. These data are presented for the aggregate blind read from the phase2 and 3 studies.

Table 41: Pooled Phase 2 and Phase 3 Performance in Pediatrics

Age	N	Incidence	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
5-9y	15	47%	8	6	1	0	86%	100%	100%	89%
10-17y	48	27%	32	11	2	3	85%	92%	82%	93%

In the 5-9y group, the incidence of appendicitis was high and the number of patients low despite pooling the data.

7. Geriatric >65y

The geriatric data is also pooled across the phase 2 and 3 studies. The data is presented for the aggregate blind read.

Table 42: Pooled Phase 2 and Phase 3 Performance in Geriatrics

	N	Incidence	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
Geriatric >65	12	50%	5	6	0	1	100%	83%	86%	100%

As in the pediatric data, the number of patients is small and the incidence of appendicitis is high.

8. "Other infections"

Patients with a final institutional diagnosis of "other infection" included diverticulitis, cholecystitis, gastroenteritis, urinary tract infections and many more. Some of these were surgical cases and some were not. These cases were examined in order to look at the performance of the scan in patients without appendicitis but with another type of infection or inflammation. These data are also pooled data across the phase 2 and 3 studies and will be presented for both the onsite reads and the aggregate blind reads.

Table 43: Pooled Phase 2 and Phase 3 Performance in Patients with a Final Institutional diagnosis of "Other Infection"

	N	Incidence	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
Onsite reads	30	0%	21	0	0	9	-	70%	-	100%
Aggregate blind	30	0%	17	0	0	13	-	57%	-	100%

There were 33 patients with a final institutional diagnosis of "other infection". Three of these patients had appendicitis and other infections and were therefore not included in this analysis.

For the onsite group, 4 of 9 patients with a final diagnosis of other infection and a false positive read for appendicitis went to surgery. The final diagnosis and disposition is listed below.

Table 44: Phase 2 and Phase 3 Onsite Read - Final Diagnosis and Disposition in Patients with a Diagnosis of "Other Infection"

Site	Patient #	Diagnosis	Surgery
Phase 2 study			
B	3	Crohn's/Gastroenteritis	No
B	7	PID/Ileitis	No
Phase 3 Study			
A	5	UTI	No
A	15	Ruptured Bladder	Yes
A	21	Peri-appendicitis	Yes
A	34	Enteritis	No
B	12	Ovarian CA/Abscess	Yes
C	3	Crohn's	Yes
I	8	Gastroenteritis	No

Only one of the four patients that went to surgery may not have needed surgery. This was the patient A-21 with periappendicitis but no evidence of actual appendicitis. This was a pathology reading.

For the Aggregate blind read, there is an increase in the number of false positive readings. Patient B-12, which was read as a false positive by the onsite readers, was not read as a false positive by the blinded aggregate read.

Table 44: Phase 2 and Phase 3 Aggregate Blind Read - Final Diagnosis and Disposition in Patients with a Diagnosis of "Other Infection"

Site	Patient #	Diagnosis	Surgery
Phase 2 study			
A	36	Colitis	No
B	3	Crohn's/Gastroenteritis	No
B	7	PID/Ileitis	No
Phase 3 Study			
A	5	UTI	No
A	15	Ruptured Bladder	Yes
A	21	Peri-appendicitis	Yes
A	23	Colitis	No
A	31	Diverticulitis	No
A	34	Enteritis	No
C	3	Crohn's	Yes
H	34	Ruptured Diverticulum	Yes
I	8	Gastroenteritis	No
J	9	Colonic Mass	Yes

For the aggregate blind read, 5 of the FP read patients went to surgery. Other than A 21 as previously discussed, all had reasonable indications for surgery.
For both the onsite readers and the aggregate blind read there is a high rate of false positive reads in those patients that ultimately had another site of infection or

inflammation other than appendicitis. This is of critical importance clinically when interpreting positive scans in the possible presence of other infections. As demonstrated by the cases from these studies, a positive scan alone was not an adequate indication to take a patient to surgery, but was used in context with all the available clinical data.

The sponsor also looked at "other infections". This was based on how the scans were read. The scans were primarily read as positive or negative. If the scan was positive, the reader would decide based on predefined criteria if the scan was positive for appendicitis or positive for another infection. This study was not designed to demonstrate the performance of the scan in patients with abdominal infections of any source, but was designed to look at specifically atypical appendicitis. The performance of the scan in patients with abdominal infections which includes those with appendicitis is shown in the table below. The onsite read is based on the elimination of the first two cases (considered training cases) at all but the lead site (9 out of 10 sites).

Table 46: Phase 3 Performance in Patients with LeuTech Scan Results of "Other Infection"

Phase 3	N	TN	TP	FN	FP	Sensitivity	Specificity	PPV	NPV
Onsite reads	182	89	69	7	17	91	84	80	93
Aggregate blind	200	117	60	22	1	73	99	98	84

Reviewer comment :Though LeuTech demonstrated similar sensitivity and improved specificity at identifying infections vs. no infections, this study was neither powered nor adequately designed to determine the significance or 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.

9. 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 as only positive or negative reads with no middle ground. Despite these issues and that this study was not designed to compare CT to LeuTech, LeuTech performed comparably to CT scanning in these 49 patients.

Table 47: Comparison of LeuTech and CT results, (N=49)

	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**

Table 48: Efficacy of LeuTech vs. CT Scan

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

Reviewer comment: Efficacy parameters were calculated on this small subset of patients. The tests performed comparably. Though these data are interesting and perhaps helpful for perspective they certainly do not validate or support one modality over another. This trial was not adequately powered or designed to meaningfully study and compare these two imaging agents.

c. 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 49: Distribution of Planned diagnostic procedures relative to LeuTech scanning

	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).

10. Age Group

The following table shows the performance outcome measures for the various age groups from the phase 3 study.

Table 50: Sensitivity and Specificity-Subgroups: 5-17,18-64, >65 Years, Evaluable Patients.

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.

11. Comparison of Gender Subgroups, Evaluable Patients.

Table 51 compares gender using all evaluable patients.

Table 51 Comparison of Gender Subgroups, Evaluable Patients.

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

Breaking the data down into gender subgroups revealed no differences in the performance parameters.

12. Comparison of Race Subgroups, Evaluable Patients.
Table 52 separates races into whites and all others.

Table 52: Comparison of Race Subgroups, Evaluable Patients.

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.

No significant differences within this phase 3 study were found.

13. Comparison of BMI Subgroups, Evaluable Patients.

Table 53 shows patient subgroups based on weight.

Table 53: Comparison of BMI Subgroups, Evaluable Patients.

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.

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.

14. Enrollment Order

Table 54 shows the comparison of patients by the order in which they presented.

Table 54: Enrollment Order

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.

15. Summary of Subgroup Analyses

Although the individual entrance criteria were not able to differentiate equivocal appendicitis in a consistent manner, the sum of 2-6 positive atypical findings provided a better atypical appendicitis population. The surgeon's management questionnaire also provided an important tool to select a sub-population based on disposition plan and likelihood of appendicitis that could reasonably be considered atypical. Each of these major subgroups had performance data that were comparable to the overall population. Other subgroups including patients based on their WBC count, women between 14-35, pediatric and geriatric populations all showed similar performance data. The women were selected for not having PID in the phase 3 study, and as shown in the data from those patients diagnosed with other infections, the performance may not differentiate PID from appendicitis well. The accuracy of the scan in women who may have PID is not clear. General age group, gender, race, weight (based on BMI) and enrollment order yielded no significant drop off in performance.

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 55 shows the clinical management disposition of all evaluable patients with and without appendicitis in the phase 3 trial.

Table 55: Phase 3 Clinical Management and Disposition

Pre-scan Disposition	N	Post-scan Disposition	N	Patients with Appendicitis #	(%)
Home	43	Home	36	2/36	(6%)
		Admit Obs.	2	0/2	(0%)
		Surgery	5	3/5	(60%)
Admit Obs.	113	Home	39	0/39	(0%)
		Admit Obs.	43	4/43	(9%)
		Surgery	31	25/31	(81%)
Surgery	33	Home	5	0/5	(0%)
		Admit Obs.	2	0/2	(0%)
		Surgery	26	21/26	(81%)

There is a shift to better management as is seen especially ion those patients whose initial disposition was admit for observation. Patients were safely sent home, fewer were admitted for observation, and some could directly to surgery. This improvement in disposition occurred based on the results of the scan prior to other testing, in addition to the elapse of several hours of time.

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.

Table 56 shows the clinical management decisions for the pediatric population.

Table 56: Phase 3 Pediatric Management and Disposition

Pre-scan Disposition	N	Post-scan Disposition	N	Patients with Appendicitis #	(%)
Home	15	Home	14	1/14	(7%)
		Admit Obs.	0	0/0	(0%)
		Surgery	1	0/1	(0%)
Admit Obs.	26	Home	10	0/10	(0%)
		Admit Obs.	10	0/10	(0%)
		Surgery	6	4/6	(67%)
Surgery	4	Home	0	0/0	(0%)
		Admit Obs.	0	0/0	(0%)
		Surgery	4	4/4	(100%)

2. Likelihood Estimate Comparison:

Table 57 displays the comparison of pre-LeuTech estimates of likelihood of appendicitis in the phase 3 studies.

Table 57: Phase 3 Likelihood Estimates Distribution

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. Receiver Operator Characteristics (ROC) Analysis

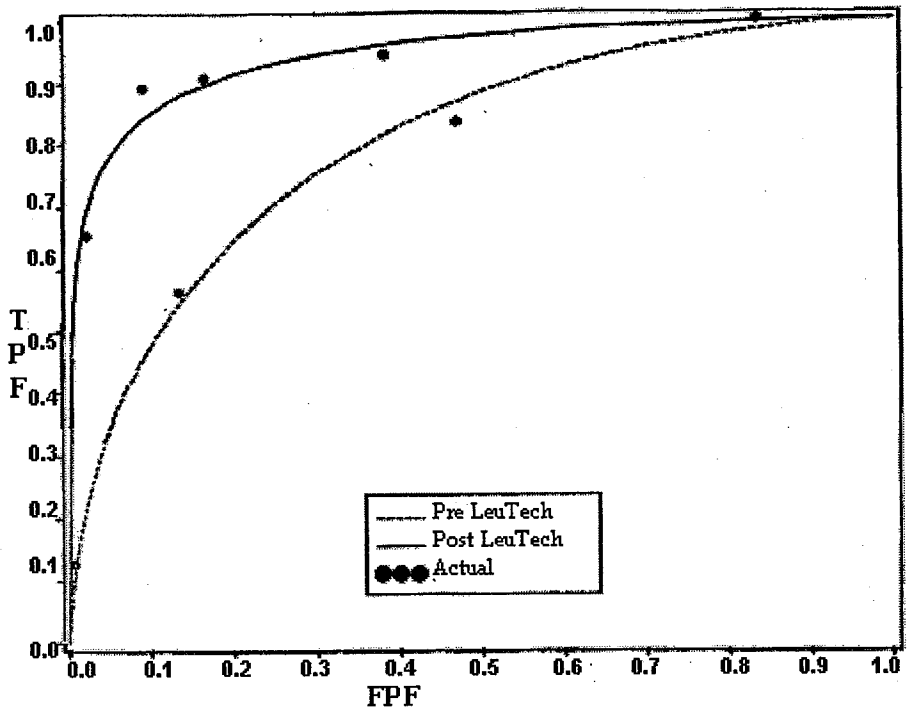
- ROC analysis was performed to compare the ROC curves pre- and post-Tc 99m LeuTechTm. The difference between the diagnostic performance pre- and post-scan was tested with the univariate z-score test, which compares the areas under the respective curves.

- 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%).



ROC Curves Pre and Post LeuTech Scan

TPF = Sensitivity FPF = 1-Specificity

I. Summary:

Patients were enrolled in the phase 3 trial with the intent to study an atypical appendicitis patient population. Defining this patient population is difficult. 203 patients were enrolled in the study using the predetermined entry criteria. These entry criteria allowed the enrollment of a wide range of patients. However, using analyses of data from other analytic approaches, demonstrated that the majority of the patients enrolled in the study presented with atypical appendicitis. The data from this trial were analyzed not only for the entire patient population studied, but also in subsets of patients that both better reflected a true atypical appendicitis patient population, in addition to other subgroups based on their WBC counts, women in reproductive years, pediatric and geriatric patients.

- In the overall studied patient population, the sensitivity for the aggregate blinded read and the onsite reads was 75% and 90% respectively. The specificity was 93% and 87% respectively. The PPV for the aggregate blind read and the onsite read was 82% and 74% respectively, and the NPV was 90% and 95% respectively. These results demonstrate adequate performance both with the onsite readers and most importantly with the blinded readers with regard to discerning clinical efficacy for LeuTech.

- In analyses of subgroups of patients, based on having 2-6 positive entry criteria, the disposition plan of admit for observation, and the surgeon's likelihood estimate of appendicitis to better assess the "atypical" population of patients, did not affect conclusions drawn from the overall performance.

- Analyzing subgroups of patients based on WBC counts, reproductive years for women and age (pediatric and geriatric patients) did not reveal subgroups where the scan performed poorly. These groups are small however, and there was a wide range in the incidence of appendicitis leading to very small numbers of actual appendicitis in some of these groups. No definitive conclusions can be based on these small numbers. The overall performance of the scan was maintained where there were an adequate number of cases of appendicitis. In patients with a WBC count between 4,000 – 7,000/mm^3 there were only 4 cases of appendicitis but 3 of those were read as false negatives. The utility of the scan in patients with a low WBC count needs further study.

- In patients with a final institutional diagnosis of other infection, there is a much higher rate of false positive scans. This would affect the utility of the scan if there were a suspicion of another inflammatory/infectious process other than appendicitis. Women with a pelvic exam suggestive of PID were excluded from this study, so that the performance of the scan in women with this infectious process is unknown.

- The management phase of the study provides support for the clinical utility of the scan to improve management decisions. These decisions can not be based on the scan alone, but are based on the entire clinical presentation.

Section IV – Pooled Data

A. 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.

$$P_{pooled} = \frac{w_2 P_2 + w_3 P_3}{w_2 + w_3}$$

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.

Table 58: Phase 2 and 3 Summary Statistics for Age, Weight, Height and BMI

	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

Table 59: Phase 2 and 3 Distribution of Gender and Race

		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.

Table 60: Phase 2 and 3 Distribution of Signs and Symptoms Comprising Equivocal Presentation

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:

Table 61: Phase 2 and 3 Distribution of Final Institutional Diagnosis for Appendicitis/No Appendicitis and Infection/No Infection, Evaluable Patients

	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. Performance:

The performance 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..

Table 62: Phase 2 and 3 Sensitivity, Specificity, Accuracy, PPV and NPV of Blinded Readers' Evaluations of Tc 99m LeuTechTm Images for Appendicitis/No Appendicitis, Evaluable Patients

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 3 trial.

Table 63: Phase 2 and 3 Likelihood Ratios of Tc 99m LeuTechTm Images For Appendicitis/No-Appendicitis, Evaluable Patients

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
'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

The total number of patients from the polled data includes 189 from the phase 3 study and 56 from the phase 2 study.

Table 64: Phase 2 and 3 Distribution of Intended Clinical Management Decisions Prior to and Following Tc 99m LeuTechTm Imaging, Evaluable Patients

Pre-scan Disposition	N	Post-scan Disposition	N	Patients with Appendicitis #	(%)
Home	49	Home	40	2/40	(5%)
		Admit Obs.	2	0/2	(0%)
		Surgery	7	5/7	(71%)
Admit Obs.	151	Home	52	0/52	(0%)
		Admit Obs.	52	7/52	(14%)
		Surgery	47	40/47	(85%)
Surgery	45	Home	7	0/7	(0%)
		Admit Obs.	2	0/2	(0%)
		Surgery	36	29/36	(81%)

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.

Table 65: Phase 2 and 3 Distribution of Estimates of Likelihood of Appendicitis Pre- and Post-Tc 99m LeuTechTm Evaluable Patients

	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:

As in the phase 3 data already presented, there was no significant differences noted in the pooled data with regard to subgroups based on age, gender, race or weight. The only additional subgroup of patients that will be presented are those that received antibiotics. A suspicion that antibiotics may affect the sensitivity of the scan based on treating the infection could be raised. In patients that received antibiotics within 24 hrs. of their scan, there was a statistically significant fall off in the specificity, not the sensitivity, for both the onsite readers and the blinded offsite readers. These data are presented below.

Table 66: Phase 2 and 3 Comparison of Antibiotic Use Subgroups, Evaluable Patients

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.
[1]Blind-read aggregate estimates based on weighted 98-004 and 97-003 estimates.

Several observations can be made:

- 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 Institutional 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 (this data was presented in the performance section of the phase 3 study):
  - 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.

Reviewer 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.

Section V - Safety

A. Introduction

Safety was assessed in terms of the occurrence of adverse events, changes in clinical laboratory parameters (chemistry, hematology, and urinalysis), changes in vital sign parameters and assessment of HAMA response.

B. Extent of Exposure

The number of patients exposed to the product both within the company's development program and in other studies are listed below.

Table 67: Safety Extent of Exposure.

Number Of Subjects	All Subjects in All Studies	All Subjects In Palatin IND Studies	
		Single Injection	**Multiple Injection**
Entered (Male/Female)	439 202/237	293 120/173	30 15/15
Received Study Drug (Male/Female)	439 202/237	293 120/173	30 15/15
Eligible for Safety Evaluations (Male/Female)	439 202/237	293 120/173	30 15/15
Age (yr.): Mean (Range)	34.1 (5.2-91.4)	33.5 (5.2-91.4)	33.8 (20.9-57.6)
Anti-CD15 IgM Antibody Dose (ug): Mean (Range)	120.1 (N=409)[1,2] (32.5-250.0)	120.7 (32.5-250.0)	125[1]
Anti-CD15 IgM Antibody Dose (ug/kg): Mean (Range)	1.8 (N=387)[2,3] (0.6-4.2)	1.8 (N=292)[3] (0.8-4.2)	1.7 (0.8-2.6)
Radioactive Dose (mCi): Mean (Range)	14.5 (N--373)[4] (1.1-33.0)	15.4 (4.2-33.0)	-----

[1] Only the first injection for subjects in Study 99-001 included; each subject in that study also received a second injection of 125 ug.
[2] Antibody dose was not recorded for 30 patients in Study 95-001. C
[3] Body weight was not recorded for all patients injected.
[4] Radioactive dose was not recorded for 6 patients in Study 95-001; 60 subjects (30 in Study 97-001 and 30 in Study 99-001) received decayed Tc 99m LeuTech.

C. Demographics

Demographic summary of patients who have received the product is listed below.

Table 68: Safety Demographic Summary

		All Subjects in All Studies	All Subjects in Palatin IND Studies	
			Single Injection	Multiple Injection
Age (Years)	N	439	293	30
	Minimum	5.2	5.2	20.9
	Maximum	91.4	91.4	57.6
	Median	31.0	29.0	31.2
	Mean	34.1	33.5	33.8
	SD	17.0	19.0	10.9
Age Category N (%)	5-9	16(4)	15(5)	0(0.0)
	10-17	50(11)	49(17)	0(0.0)
	18-64	343(78)	202(69)	30(100)
	> 65	30(7)	27(9)	0(0.0)
Gender N (%)	Female	237(54)	173(59)	15(50)
	Male	202(46)	120(41)	15(50)
Race N(%)	White	251 (57)	201 (69)	25(83)
	Black	39(9)	22(8)	2(7)
	Hispanic	94(21)	60(20)	0(0)
	Other	22(5)	10(3)	3(10)
	Not specified	33(8)	0	0
Height (cm)	N	350	290	30
	Minimum	104.1	104.1	152.4
	Maximum	198.1	198.1	190.5
	Median	167.6	167.6	174.0
	Mean	165.8	165.1	172.2
	SD	13.6	14.0	9.9
Weight (kg)	N	410	292	30
	Minimum	21.4	21.4	48.2
	Maximum	170.0	139.5	161.4
	Median	68.5	68.2	73.6
	Mean	70.8	69.8	77.3
	SD	21.0	20.4	21.6
Body Mass Index (BMI)	N	350	290	30
	Minimum	12.6	12.6	19.2
	Maximum	49.6	46.7	49.6
	Median	24.3	24.4	24.4
	Mean	25.4	25.3	25.9
	SD	5.7	5.7	6.2

Subjects enrolled in the clinical studies ranged in age from 5 years to 91 years, with a median age of 31 years. Sixteen (4 %) subjects were between 5 years and 9 years old, 50 (11%) were between 10 years and 17 years, 343 (78 %) were between 18 years and 64 years, and 30 (7 %) were 65 or older. Two hundred thirty-seven (54%) were female and 202 (46%) were male. There were 251 (57 %) whites, 39 (9 %) blacks, 94 (21 %) Hispanics, and 22 (5%) "Other"; race was not specified for 33 subjects. BMI ranged from 12.6 to 49.6, with an average of 25.4. The three subject groupings were similar with respect to mean age, height, weight and BMI, and with respect to gender. Unlike the other two groupings, most of the multiple injection subjects were white, and none were younger than 18 years or older than 64 years.

D. Concomitant Medications

Medications were coded according to the WHO drug dictionary, and the Level 3 Medication Classification was used to group medications. A summary of concomitant medication data according to Level 3 classes or appropriate grouping of Level 3 classes is presented below.

Table 69: Safety Concomitant Medications Received by Subjects.

MEDICATION CLASS	All Subjects in All Studies' (N=353) N (%)	All Subjects in Palatin IND Studies	
		Single Injection (N=293) N (%)	Multiple Injection (N=30) N (%)
Antibiotics	54(15)	51(17)	3(10)
NSAII)s	52(15)	33 (11)	16(53)
Opioids	58(16)	56(19)	2(7)
Other analgesics and antipyretics	77(22)	56(19)	17(57)
Psychotherapeutic	47(13)	44(15)	3(10)

'Not including Studies 95-001 and Gratz-Becker

Including all subjects with medication data available, 54 (15%) received antibiotics and 52 (15%) received NSAIDs. 58 (16%) subjects received opioids, and 77 (22%) subjects were taking other analgesics and antipyretics. 47 (13%) subjects received psychotherapeutic medications,

E. Adverse Events

Adverse event (AE) data were collected for all subjects in all studies. Assessments were performed at various time-points following injection of Tc, 99m LeuTech. Data were coded according to the COSTART dictionary of terms.

1. Deaths, Discontinuations for Adverse Events, and Serious Adverse Events

No deaths, serious AEs or any other significant A-E occurred in any subject enrolled in any of the clinical trials included in this summary. No subjects discontinued participation due to AEs.

2. Adverse Event Summary

A total of 39 adverse events were reported in 30 of 439 subjects (6.8%). Adverse events are summarized by COSTART preferred term and body system below.

Table 70: Safety Summary Of Adverse Events by COSTART Term and Body System.

Body System	COSTART Term	All Subjects in All Studies (Total Subjects=439) N (%)	All Subjects in Palatin IND Studies	
			Single Injection (Total Subjects=293) N (%)	Multiple Injection (Total Subjects=30) N (%)
All Systems	ANY EVENT	30(7)	21(7)	7(23)
Body as a Whole	ANY EVENT	10(2)	6(2)	2(7)
	HEADACHE	2(1)	2(1)	0(0)
	PAIN INJECT SITE	2(1)	1(<1)	0(0)
	ASTHENIA	1(<1)	1(<1)	0(0)
	INJECT SITE REACT	1(<1)	1(<1)	0(0)
	MALAISE	1(<1)	0(0)	1(3)
	PAIN	2(1)	1(<1)	1(3)
	PAIN ABDO	1(<1)	0(0)	0(0)
	PAIN CHEST	1(<1)	1(0<1)	0(0)
Cardiovascular	ANY EVENT	13(3)	12(4)	1(3)
	VASODILAT	11(3)	10(3)	1(3)
	SYNCOPE	2(1)	2(1)	0(0)
Digestive	ANY EVENT	1(<1)	1(<1)	0(0)
	DIARRHEA	1(<1)	1(<1)	0(0)
Hemic and	ANY EVENT	1(<1)	0(0)	1(3)
Lymphatic	ECCHYMOSIS	1(<1)	0(0)	1(3)
Musculoskeletal	ANY EVENT	1(<1)	0(0)	1(3)
	JOINT DISORDER	1(<1)	0(0)	1(3)
Nervous	ANY EVENT	5(1)	3(1)	2(7)
	DIZZINESS	2(1)	2(1)	0(0)
	PARESTHESIA	3(1)	1(<1)	2(7)
Respiratory	ANY EVENT	7(2)	5(2)	2(7)
	DYSPNEA	4(1)	4(1)	0(0)
	PHARYNGITIS	2(1)	0(0)	2(7)
	RHINITIS	1(<1)	1(<1)	0(0)
Total Number of Events		39	28	9

The most frequently reported AE was vasodilatation, experienced by 11 (3 %) subjects. Dyspnea was reported by 4 (1%) subjects and paresthesia was reported by 3 (1%) subjects. Headache, pain, pain at injection site, syncope, pharyngitis and dizziness were reported in 2 (1%) subjects each. Asthenia, injection site reaction, malaise, abdominal pain, chest pain, diarrhea, ecchymosis, joint disorder and rhinitis were reported in 1 (<1%) of subjects. The greater incidence of AEs in the multiple injection subjects may have been due to the longer AE surveillance period (7 weeks) in Study 99-00 1.

Severity of AEs was classified as mild, moderate or severe. Thirty-one (3 1) events were mild in severity, 6 were moderate, 1 (injection site pain) was specified as moderate-severe, and 1 (abdominal pain) was not specified. The moderate or severe events are summarized by COSTART term and body system below.

Table 71: Safety Summary of Moderate or Severe Adverse Events by COSTART Term and Body System.

Body System	COSTART	All Subjects in All Studies (Total Subjects=439) N	All Subjects in Palatin IND Studies	
			Single Injection (Total Subjects 293) N (%)	Multiple Injections (Total Subjects = 30) N (%)
All Systems	ANY EVENT	7(2)	5(2)	1(3)
Body as a Whole	ASTHENIA	1(<1)	1(<1)	0(0)
	HEADACHE	2(1)	2(1)	0(0)
	PAIN	1(<1)	1(<1)	0(0)
	PAIN INJECT SITE	1(<1)	0(0)	0(0)
Cardiovascular	VASODILAT	1(<1)	1(<1)	0(0)
Nervous	PARESTHESIA	1(<1)	0(0)	1(3)
Total Number of Events		7	5	1

Of the 39 adverse events, 20 in 14 subjects were considered possibly or probably related to study drug (relationship was not specified for 2 events). They are summarized below.

Table 72: Safety Summary of Adverse Events Considered Possibly or Probably Related To Study Drug by COSTART Term and Body System.

Body System	COSTART	All Subjects in All Studies (Total Subjects=439) N(%)	All Subjects in Palatin IND Studies	
			Single Injection (Total Subjects 293) N(%)	Multiple Injections (Total Subjects 30) N(%)
All Systems	ANY EVENT	14(3)	12(4)	2(7)
Body as a Whole	HEADACHE	1(<1)	1(<1)	0(0)
	INJECT SITE REACT	1(<1)	1(<1)	0(0)
	PAIN CHEST	1(<1)	1(<1)	0(0)
	PAIN INJECT SITE	1(<1)	1(<1)	0(0)
Cardiovascular	VASODILAT	11(3)	10(3)	1(3)
Hemic and Lymphatic	ECCHYMOSIS	1(<1)	0(0)	1(3)
Nervous	DIZZINESS	1(<1)	1(<1)	0(0)
	PARESTHESIA	1(<1)	1(<1)	0(0)
Respiratory	DYSPNEA	2(1)	2(1)	0(0)
Total Number of Events		20	18	2

F. Clinical Laboratory Assessments

Clinical laboratory measurements were obtained in 4 clinical trials. In the phase1 clinical pharmacology study, 10 normal volunteers had hematology, chemistry and urinalysis parameters pre-injection and at 1 hour, 4 hours and 18-24 hours post-injection. In addition, white blood cell (WBC) counts and differential assessments were performed at 3, 5.5 10, 15, 30 and 45 minutes post-injection. In both the phase 3 appendicitis study with 203 patients and in a phase 2 osteomyelitis study of 24 patients, hematology and chemistry parameters pre-injection and at 2 hours post-injection were obtained. In the

Phase I repeat-injection HAMA study 30 normal volunteers had hematology and chemistry parameters measured immediately prior to each injection and at 7 days and 28 days after the second injection.

1. Clinical Laboratory Parameters: Clinically Significant Changes from Baseline

In each of the studies, study investigators were to evaluate post-injection changes in clinical laboratory parameters from baseline for clinical significance.

Clinically significant changes from baseline are presented by subject below.

Table 73: Safety Clinically Significant Laboratory Parameter Changes From Baseline, All Subjects with Laboratory Assessments.

Study Number, Site and Subject Number	Parameter (Normal Range)	Baseline Value	Post-injection Value	Time Post-Injection (hh:mm)
97-002, Subject 1-03	LDH (313-618 U/L)	556	1084	01:10
98-004, Patient D-21	AST (11-39 UIL)	61	154	31:26
	ALT (6-42 UIL)	37	97	31:26
98-004, Patient H- 10	Hgb (12.0-16.0 g/dL)	14.7	11.2	12:27
	Hct (38.0%-47.0%)	42.8	32.6	12:27
99-001, Subject 25	LDH (90-225 U/L)	182	1496	167:33[1]
	AST (5-45 U/L)	31	132	167:33[1]

[1]Time following second injection; second injection was 21 days after first injection

A total of 7 clinically significant changes in laboratory parameters were reported in 4 of 242 subjects (2%) enrolled in the studies. The change in LDH in Subject 1-03 (Study 97-002) was determined to be a laboratory error. The changes in AST and ALT in Patient D-21 (Study 98-004) and in hemoglobin (Hgb) and hematocrit (Hct) in Patient H-10 (Study 98-004) were attributed to disease with no follow-up required. The only subject who experienced clinically significant changes in laboratory parameters possibly attributed to Tc 99m LeuTech was Subject 25 in Study 99-001. This subject experienced an elevation in AST and LDH one week after the second injection. Values for both measurements returned to normal range at 4 weeks following the second injection without any treatment (AST = 29 U/L and LDH = 201 U/L). The investigator noted that this elevation in liver enzymes was unexpected and clinical and laboratory follow-up revealed no cause. Therefore, he was unable to exclude the possibility of relationship to the injection of LeuTech.

2. Clinical Laboratory Parameters: Range Shifts

Clinical laboratory measurements post-injection were categorized according to each laboratory's normal range as low (less than the lower limit), normal (within the normal range), or high (greater than the upper limit). In Study 98-004 (Phase 3 Appendicitis) and Study 98-005 (Phase 2 Osteomyelitis), laboratory measurements were performed 2 hours post-injection. Bowker's or McNemar's test was used to test the pre- versus post-injection distributions (shift tables) for symmetry. A summary of the statistically significant findings is provided below.

Table 74: Safety Statistically Significant Shifts in Laboratory Parameters at 2 Hours, All Patients in Phase 3 Appendicitis and Phase 2 Osteomyelitis Studies

Parameter	Number of Patients with Shift[1]	Shift Upward		Shift Downward		
		Low to Normal	Normal to High	Normal to Low	High to Normal	High to Low
Hematology						
WBCs	32 (N=184)	2	5	5	20	0
Neutrophils	36 (N=144)	5	3	6	21	1
Hemoglobin	27 (N=184)	6	1	20	0	0
Clinical Chemistry						
Total Protein	27 (N=171)	2	0	16	8	1
BUN	18 (N=188)	2	0	13	3	0

[1]N is total number of patients in shift table, i.e., patients with both baseline and 2-hour measurements.

For each parameter, there was a significantly higher incidence of downward shifts post-injection. Some changes in laboratory parameters may have been due to increases in hydration from intravenous fluids given in a hospital emergency room or diagnostic imaging area. Overall, the clinical laboratory parameter changes were small and none of the changes were considered to be clinically significant. No change, other than those of WBCs and neutrophils, was thought to represent a treatment-related trend, and changes for WBCs and neutrophils were of a small magnitude in this non-neutropenic patient population.

Similar downward shifts in WBCs and granulocytes were observed for the Phase 1 study in 10 normal volunteers (Study 97-002) during the first 30 minutes post- injection. Upward shifts in the relative percent of lymphocytes and monocytes were also noted in this time period, and could be attributed to the reduction in absolute granulocyte count. There were fewer shifts at 1 hour and by 4 hours, there was no evidence of downward shifts. These shifts corresponded to the transient decrease in WBC count and percent granulocytes and appeared to be related to hepatosplenic sequestration of the granulocytes. The investigator did not consider these transient shifts clinically meaningful. No other shifts in hematology parameters were statistically significant.

Table 75: Safety WBC, Granulocyte and Lymphocyte Counts Phase 1 Study

Parameter	Baseline	3 min	5 min	10 min	15 min	30 min	45min	1 hr	4 hr	18-24 hr
WBC(10^3/uL)	5.7	5.1	4.3	3.6	3.2	3.6	4.2	5.1	5.2	-
Granulocytes(%)	57%	-	52%	39%	35%	34%	45%	47%	-	-
Granulocytes(10^3/uL)	3.3		2.2	1.4	1.1	1.2	1.9	2.4	-	-
Lymph(%)	31%	33	37%	48%	51%	47%	41%	41%	-	33%
Lymph(10^3/uL)	1.8	1.7	1.6	1.7	1.6	1.7	1.7	2.1	-	-
Worse Individual Cases Reported (Patient # 4 - 21y F)										
WBC(10^3/uL)	3.8	3.7	3.6	3.2	2.4	2.5	2.5	3.0	4.3	4.3
Granulocytes(%)	38%	25%	24%	20%	12%	6%	2%	5%	-	-
Granulocytes(10^3/uL)	1.4	0.9	0.9	0.6	0.3	0.2	0.05	0.2	-	-
Lymph(%)	53%	64%	67%	67%	76%	76%	86%	84%	-	-
Lymph(10^3/uL)	2.0	2.4	2.4	2.1	1.8	1.9	2.2	2.5	-	-
Patient # 7 – 36 F										
WBC(10^3/uL)	3.8	-	-	2.4	2.3	2.2	2.4	2.8	4.9	4.5
Granulocytes(%)	52%	-	-	31%	14%	15%	14%	30%	-	48%
Granulocytes(10^3/uL)	2.0	-	-	0.7	0.3	0.3	0.3	0.8	-	2.2
Lymph(%)	31%	-	-	52%	60%	58%	64%	60%	-	37%
Lymph(10^3/uL)	1.2	-	-	1.2	1.3	1.3	1.5	1.7	-	1.7

This data had numerous values that were unreported or not obtained. There was a drop in the total WBC, which appears to be driven by the drop in the total neutrophil count. This was a transient drop with a recovery in 1 hours. The worse individual case started with a WBC of 3.8×10^3/uL and an absolute neutrophil count of 1.4×10^3/uL. This neutrophil count dropped to a low of 0.05×10^3/uL at 45 min then started to recover though the 4 hr and 18-24 hr data are not reported.

Reviewer comment: There are no data on the performance of LeuTech in neutropenic patients. This issue was raised and noted in the Medical Imaging and Device Advisory Committee. The two patients with the lowest WBC were both in a phase 1 trial and both had significant drops in their absolute neutrophil count. Though this affect appears to be transient, further study will be required to assess the safety and performance of this product in neutropenic patients.

G. Human Anti-Mouse Antibody (HAMA) Response

1. HAMA Response Following Single Injection

Under BB-IND 2995, HAMA response was evaluated in Study 97-001 (clinical pharmacology, 30 normal volunteers) and in four patients in Study 95-001. 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 LeuTech and at 3 weeks to 4 weeks post-injection. Subjects in Studies 97-001 and 95-001 were re-tested at 3 months to 4 months for HAMA response. Patients in Study 98-004 who had a positive response at 3 weeks to 4 weeks were to be re-tested for HAMA response at 12 weeks to 16 weeks post-injection. The table below summarizes the distribution of post-injection HAMA response.

2. Distribution of Positive HAMA Response Following Single Injection.

Table 76: Safety HAMA following single injection

Study	3 - 4 Weeks	12 - 16 Weeks
	Proportion Positive	**Proportion Positive**
Study 97-001	0/30 (0)	0/30 (0)
Study 98-004[1]	0/20 (0)	-
Study 95-001	0/4 (0)	0/4 (0)
All	0/54 (0)	0/34 (0)

[1]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.

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

3. HAMA Response Following Multiple Injections

Under BB-IND 7996, HAMA response was evaluated in Study 99-001 (30 normal volunteers). This study was an evaluation of HAMA response following two injections of LeuTech three weeks apart. The results from this study were not included in the original BLA filing, but they were provided in the 120-Day Safety Update. A baseline control serum sample was collected from each subject, followed by the first LeuTech injection. Approximately 3 weeks later, another serum sample was collected followed by the second LeuTech injection. One week and 4 weeks after the second LeuTech injection, additional serum samples were collected from each subject. Any serum sample collected post- LeuTech administration having a HAMA titer greater than or equal to 4X the baseline value (prior to the first LeuTech administration) for the same subject was considered positive (Greenman et al, 1991). Five of the 30 subjects exhibited positive HAMA responses at one or more post-injection times and they are presented below.

Table 77: Safety Subjects Having Positive HAMA Response at One or More Post injection Times (HAMA Values in ng/mL

Subject	Baseline	Pre-Dose 2	Follow-up 1	Follow-up 2
08	5	8	14	31*
23	7	8	13	228*
27	7	17	140*	270*
28	5	20*	24*	10
	7	12	35*	450*

* HAMA titer post-LeuTech $\geq$ 4X baseline value (positive HAMA response)

Two of the five subjects had marginal responses (Subjects 08 and 28) and three subjects had moderate responses (Subjects 23, 27 and 30). None of the responses were considered strong (greater than 1000 ng/mL).

H. Vital Signs

1. Changes in Vital Signs from Baseline

Vital signs were measured in six of the clinical trials. The vital signs were assessed at varying time points depending on the study, but in most cases they were measured immediately pre-injection and at 5 minutes, 30 minutes and 1 hour post-injection. A summary of mean changes at these time-points is provided below.

Table 78: Safety Summary of Mean Changes in Vital Signs.

	All Subject[1] (N)	All Subjects in Palatin IND Studies	
		Single Injection (N)	Multiple Injection[3] (N)
Systolic Blood Pressure (mm. Hg)			
Immediately Pre-Injection	121.2 (N=384)	121.2 (N=293)	118.4 (N=30)
Change @ 5 Min Post[2]	-0.8* (N=378)	-0.9* (N=292)	-0.2 (N=30)
30 Min Post	-0.4 (N=381)	-0.1 (N=291)	-0.4 (N=30)
1 Hr Post	0.1 (N=370)	0.5 (N=283)	0.6 (N=30)
Diastolic Blood Pressure (mm Hg)			
Immediately Pre-Injection	72.5 (N=384)	71.6 (N=293)	76.2 (N=30)
Change @ 5 Min Post[2]	-1.1* (N=378)	-1.2* (N=292)	-0.5 (N=30)
30 Min Post	-1.0 * (N=381)	-0.9* (N=291)	-1.3 (N=30)
1 Hr Post	-0.8 * (N=370)	-0.7* (N=283)	-0.9 (N=30)
Pulse Rate (bpm)			
Immediately Pre-Injection	78.7 (N=383)	78.6 (N=292)	68.5 (N=30)
Change @ 5 Min Post[2]	0.2 (N=377)	0.1 (N=291)	0.6 (N=30)
30 Min Post	-0.5 (N=380)	-0.3 (N=290)	-0.4 (N=30)
I Hr Post	-1.3 * (N=369)	-1.4 * (N=282)	0.6 (N=30)
Body Temperature (Oral °C)			
Immediately Pre-Injection	37.1 (N=372)	37.1 (N=282)	36.9 (N=30)
Change @ 5 Min Post[2]	0.0 (N=365)	0.0 (N=281)	0.1 (N=30)
30 Min Post	0.0 (N=369)	0.0 (N=280)	0.0 (N=30)
I Hr Post	0.0 (N=357)	0.0 (N=271)	0.0 (N=30)

[1]Vital signs not collected for subjects in Study 97-001 and not available for patients in the Gratz-Becker study.
[2] Includes change at end of injection for Study 95-001.
[3]Includes data following first injection only.
*Statistically significant change ($p<.05$) according to Wilcoxon's signed-rank test.

Statistically significant decreases in systolic and diastolic blood pressures were noted following injection, and a statistically significant decrease in pulse rate was noted at 1 hour post-injection. However, the changes were small and not clinically significant.

2. Clinically Significant Changes in Vital Signs

For studies under Palatin INDs, clinical significance of changes in vital signs was defined in the protocols as any change (increase or decrease) that met any of the following criteria:

systolic blood pressure > 35 mm Hg diastolic blood pressure > 25 mm. Hg
pulse rate > 20 beats per minute

In addition, any other changes the investigator considered clinically significant were noted. Any clinically significant change was assessed by the investigator for its possible relationship to the study drug.

The criteria defining clinically significant changes in vital signs also were applied retrospectively to the vital sign data for Study 95-001 (BB-U~D 2995) to identify clinically significant changes.

Across all studies, 20 subjects experienced protocol-defined clinically significant changes in vital signs from baseline values. The changes in 18 subjects were not related to Tc 99m LeuTech in the opinion of the investigators. Relationship of changes to Tc 99m LeuTech in 2 subjects in Study 95-001,noted on retrospective review of vital sign data, was not specified. The frequency of clinically significant changes from baseline is summarized below.

Table 79: Safety Incidence of Clinically Significant Changes in Vital Signs.

Type of Vital Sign Change Post-Injection	All Subjects in All Studies[1] (N = 383) N (%)	All Subjects in Palatin IND Studies	
		Single Injection (N 292 Subjects) N (%)	Multiple Injection (N 30 Subjects) N (%)
Heart Rate Decrease >20 beats/min	5(l)	4(l)	0(0)
Heart Rate Increase >20 beats/min	7(2)	5(2)	2(7)
BP Decrease Systolic > 35 mm Hg Diastolic > 25 mm Hg	3(1)	2(1)	0(0)
BP Increase - Systolic > 35 mm Hg Diastolic > 25 mm Hg	5(1)	5(2)	0(0)

[1]Vital signs were not collected for subjects in Study 97-001 and were not available for patients in the Gratz-Becker study

Of 383 subjects with vital sign data both pre- and post-injection, protocol-defined changes were observed as follows: 5 (1%) experienced a significant decrease in heart rate

and 7 (2%) experienced a significant increase in heart rate; 3 subjects (1%) experienced a significant decrease in blood pressure and 5 subjects (1%) experienced a significant increase in blood pressure. The incidence of clinically significant vital signs changes was similar for all three subject-groups.

I. COMPARISON OF AGE SUBGROUPS

Incidence of adverse events and clinically significant changes from baseline for clinical laboratory parameters and vital signs were summarized for the following age subgroups: 5-9 years, 10-17 years, 18-64 years and ≥ 65 years. Results are summarized below.

Table 80: Safety Proportion of Subjects Reporting One or More Adverse Events, by Age Group.

	All Subjects in All Studies Proportion (%)	All Subjects in Palatin Studies	
		Single Injection Proportion (%)	Multiple Injection Proportion
5-9 Years	1/16(6)	1/15 (7)	0(0)
10-17 Years	0150(0)	0/49(0)	0(0)
18-64 Years	29/343 (9)	20/202 (10)	7/30(23)
≥ 65 Years	0/30(0)	0/27(0)	0(0)

Overall, 30 of 439 subjects (6.8%) reported one or more AEs. One AE was reported in the age group of 5-9 years (1/16; 6.3%). Twenty-nine subjects in the age group of 18-64 reported one or more A-Es (29/343; 8.5%). No AEs were reported in the age group of 10-17 years (0/50; 0%), nor in subjects 65 years of age or older (0/ 19; 0%).

Table 81: Safety Proportion of Subjects Having a Clinically Significant Change from Baseline in One or More Laboratory Parameters, by Age Group.

	Subjects in Palatin IND Studies	
	Single Injection Proportion (%)	Multiple Injection Proportion(%)
5-9 Years	0/11(0)	0/0(0)
10-17 Years	0/36(0)	0/0(0)
18-64 Years	3/146(2)	1/30(3)
≥65 Years	0/19(0)	0/0(0)

Only 4 of 242 subjects (2%) had a clinically significant change from baseline in laboratory parameters and all subjects were between the ages of 18-64 years. The

laboratory parameter change in one subject was attributed to laboratory error, and the changes in two subjects were attributed to disease. The only subject who experienced clinically significant changes in laboratory parameters possibly attributed to Tc 99m LeuTech was in the multiple-injection HAMA study. This subject experienced elevations in AST and LDH one week after the second injection. Both values returned to normal at 4 weeks after the second injection without treatment.

Table 82: Safety Proportion of Subjects Having a Clinically Significant Change from Baseline in One or More Vital Signs, By Age Group.

	All Subjects in All Studies Proportion (%)	All Subjects in Palatin IND Studies	
		Single Injection Proportion (%)	Multiple Injection Proportion (%)
5-9 Years	1/16(6)	0115(0)	0/0(0)
10-47-Years	3/49(6)	3/49(6)	0/0(0)
18-64 Years	13/290 (5)	10/201 (5)	2/30(7)
≥65 Years	3/28(11)	3/27(11)	0/0(0)

Twenty of 383 subjects (5%) reported one or more clinically significant changes from baseline in vital signs. Across all studies, changes were reported for 1 subject in the age group of 5-9 years (1/16; 6%) and for 3 subjects in the 10-17 year age group (3/49; 6%). Thirteen subjects in the 18-64 year age group (13/290; 5%) and three subjects in the 65 years of age or older group (3/28; 11%) reported one or more clinically significant changes. The percentage of clinically significant changes reported was similar for all three age groups. No change in vital signs was thought to represent an age-related trend.

J. Safety Conclusions

Safety data were summarized for 439 subjects enrolled and dosed in 8 trials. Subjects ranged in age from 5.2 years to 91.4 years, with an average age of 34.1 years. Sixteen (4%) subjects were between 5 years and 9 years old, 50 (11%) were between 10 years and 17 years old, 343 (78%) were between 18 years and 64 years, and 30 (7%) were 65 years or older. Two hundred thirty-seven (237; 54%) were female and 202 (46%) were male. There were 251 (57%) whites, 39 (9%) blacks, 94 (21%) Hispanics, and 19 (5%) "other".

Of the 439 subjects, 293 subjects participated in studies conducted under a Palatin IND that involved a single injection and 30 subjects participated in a Palatin IND study that involved two injections.

All subjects received a single injection of Tc 99m LeuTech, except for the subjects enrolled in Study 99-001, who received two injections of decayed Tc 99m LeuTech to evaluate HAMA response. Subjects enrolled in Study 97-001 received a single injection of decayed Tc 99m LeuTech to evaluate HAMA response. The average antibody dose was 120.1 ug (range 32.5 ug to 250 ug). Excluding the subjects who received decayed Tc 99m LeuTech in studies 97-001 and 99-001, the radioactive dose ranged from 1.1 mCi to 33.0 mCi, with a mean of 14.5 mCi.

No deaths, serious AEs or any other significant AE occurred in any subject enrolled in any of the clinical trials included in this document. No subjects discontinued participation due to AEs.

Thirty subjects (of 439; 7%) reported a total of 39 AEs. Fourteen subjects (3% of 439 subjects) experienced a total of 20 AEs that were considered possibly or probably related to the study drug. The most frequently reported AE was vasodilatation, experienced by 11 (3%) subjects. Dyspnea was reported by 4 (1%) subjects and-paresthesia was reported by 3 (1%) subjects. Headache, pain, syncope, pain at injection site, pharyngitis and dizziness were reported in 2 (1%) subjects each. Asthenia, injection site reaction, malaise, abdominal pain, chest pain, diarrhea, ecchymosis, joint disorder and rhinitis were reported in 1 (<1%) subject each. All 11 cases of vasodilatation were considered possibly or probably related to the study drug, as were 2 cases of dyspnea, and single cases of dizziness, headache, chest pain, paresthesia, injection site pain, injection site reaction and ecchymosis. One event (injection site pain) was classified as moderate-severe and six events were classified as moderate. The remaining events were classified as mild, with the exception of one event (abdominal pain) for which severity was not specified.

Clinical laboratory parameters were measured and evaluated for changes from baseline in four studies. The only clinically significant changes in laboratory parameters that were possibly attributed to LeuTech were elevations in AST and LDH in one subject after a second injection. These elevated liver enzymes returned to baseline without treatment; clinical and laboratory follow-up revealed no cause, so the investigator was unable to exclude the possibility of relationship to the injection of LeuTech.

For the phase 3 appendicitis study and the phase 2 osteomyelitis study, statistically significant shifts downward in laboratory parameters were noted at 2 hours post-injection for WBC, neutrophils, hemoglobin, total protein and BUN. The highest incidence of shifts occurred for neutrophils and WBCs. Twenty-five of 184 (13.6%) and 28 of 133 (21.2%) patients demonstrated a negative shift in WBCs and neutrophils, respectively. In the Phase I study in 10 normal volunteers reviewed earlier, WBC and granulocyte count were measured frequently during the first hour and at 4 hours and 18-24 hours post-injection. Both WBC and granulocyte counts demonstrated decreases after Tc 99m LeuTech administration, which had recovered by 4 hours. Neutropenic patient studies need to be performed with careful monitoring of the WBC count and absolute neutrophil count.

The shifts in the other laboratory parameters (hemoglobin, total protein and BUN) were not believed to be related to study drug. They may have been due to increases in hydration from intravenous fluids given in a hospital emergency room.

None of the 54 subjects having HAMA assays before and after a single injection of LeuTech had a positive HAMA response at any time point. Five of the 30 subjects who received two injections of LeuTech exhibited positive HAMA responses. Two of the five subjects had marginal responses and three had moderate responses. None of the responses were considered strong (greater than 1000 ng/mL).

Mean changes in vital signs were evaluated at 5 minutes, 30 minutes and 1 hour post injection. Statistically significant decreases in systolic and diastolic blood pressures were noted following injection, and a statistically significant decrease in pulse rate was noted at 1 hour post-injection. However, the changes were small and not clinically significant.

In summary, Tc 99m LeuTech has been well tolerated and safe in all studied populations, including the pediatric, adult and geriatric populations, for use according to the proposed indication. Further studies will be needed to demonstrate safety in a neutropenic population.

SECTION VI – RECOMMENDATION

Based on:

- The performance of the scan in patients presenting with atypical signs and symptoms of appendicitis
- The safety profile of the scan in the data base studied

I recommend approval of this product for licensure.

Further areas of study in phase 4 would include but not be limited to:

- Increasing the safety data base. The studied population is relatively small compared to a potentially large population in which the scan could be used.
- Studying neutropenic patients in a closely monitored setting
- Expanding the data base in the geriatric patient population

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