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MEDICAL IMAGING DRUGS ADVISORY COMMITTEE

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CASET Associates, Ltd.
10201 Lee Highway, Suite 160
Fairfax, VA 22030
(703) 352-0091

PARTICIPANTS:

Committee:
Laura L. Boles Ponto, Ph.D., Acting Chairperson
University of Iowa Hospitals and Clinics

Thomas H. Perez, M.P.H., Executive Secretary
CDER, FDA

Sara J. Abramson, M.D.
Memorial Sloan Kettering Cancer Center

Richard J. Hammes, R.Ph.
University of Wisconsin Hospitals and Clinics

Arnold W. Malcolm, M.D.
St. Joseph Medical Center, Burbank, California

Mark Tuchinsky, M.D.
Penn State University Hospital

FDA Consultants:
Jonathan Links, Ph.D.
John Hopkins University School of Hygiene and Public Health

Thomas Whalen, M.D.
Robert Wood Johnson Medical School at Camden

Eddie Hoover, M.D.
SUNY at Buffalo, Erie County Medical Center

Guests:
Robert Rothstein, M.D.
Suburban Hospital, Bethesda, Maryland

Gary Strange, M.D.
University of Illinois at Chicago, College of Medicine

Brent Blumenstein, Ph.D.
American College of Surgeons

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P R O C E E D I N G S (8:34 a.m.)

Agenda Item: Call to Order, Introductions: Laura L. Boles Ponto, Ph.D., Chair

DR. PONTO: I would call to order this meeting of the Medical Imaging Drugs Advisory Committee. I'd like to start by having the members of the committee please introduce themselves.

I am Laura Ponto. I am at the University of Iowa. I work in the Positron Emission Tomography Imaging Center as a research scientist.

DR. HOOVER: My name is Eddie L. Hoover. I'm professor and chairman of the Department of Surgery at the State University of New York at Buffalo.

DR. ROTHSTEIN: I'm Bob Rothstein. I'm a practicing emergency physician in Bethesda, Maryland.

DR. WHALEN: Tom Whalen. I'm a pediatric surgeon and professor of surgery at Robert Wood Johnson Medical School.

DR. STRANGE: I'm Gary Strange. I'm the head of emergency medicine at the University of Illinois in Chicago.

DR. AMENDOLA: Hi, my name is Marco Amendola. I'm professor of radiology at the University of Miami, Jackson Memorial Medical Center.

DR. BLUMENSTEIN: I'm Brent Blumenstein, a biostatistician with the American College of Surgeons

Oncology Group.

MR. PEREZ: I am Tom Perez. I'm the executive secretary for this meeting.

DR. TULCHINSKY: Mark Tulchinsky, one of nuclear medicine physicians at Penn State University Hospital.

DR. ABRAMSON: Sara Abramson, professor of pediatric radiology at Memorial Sloan Kettering Cancer Center.

DR. LINKS: Jonathan Links. I'm a professor at Johns Hopkins, and I'm also president of the Society of Nuclear Medicine.

DR. HAMMES: Richard Hammes. I'm director of Nuclear Pharmacy Services at the University of Wisconsin, and professor of pharmacy.

DR. MARTYNEC: Lydia Martynec. I'm the nuclear medicine physician reviewing the Palatin product for the FDA.

DR. LINDBLAD: Robert Lindblad. I'm the medical reviewer for the Palatin product for the FDA.

DR. WEISS: Karen Weiss, the director of the Division of Clinical Trial Design and Analysis at CDER at the FDA.

DR. PONTO: Thank you very much. I would like to now turn it over to our executive secretary for the meeting statements.

Agenda Item: Meeting Statement: Thomas H. Perez, M.P.H., Executive Secretary

MR. PEREZ: Good morning. The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. PONTO: At this point in time we would like to turn the meeting over to Palatin Technologies for their presentation. Mr. Putnam.

Agenda Item: Palatin Technologies, Inc.

Presentation: Introduction - Charles Putnam, Chief

Operating Office, Palatin

MR. PUTNAM: Good morning. My name is Charles Putnam. I'm the chief operating officer of Palatin Technologies. We have with us today Dr. Terry Smith, our executive director of product development. We have Dr. Rypins and Dr. Kipper. These gentlemen worked at the highest enrolling site in our Phase 3 trial, and also were involved in our Phase 2 trial, and as such, they are quite capable of discussing the performance LeuTech in the clinic. And also presenting for us will be Dr. Karen McElvany, who works for Certus International, the CRO that handled all of our company-sponsored clinical trials.

In addition, in the event that questions might arise, we have with us today Dr. Robert Caretta, who is the president of the Society of Nuclear Medicine, and also an investigator on our Phase 3 trial at Sutter-Roseville, which as I recall is our second highest enrolling site. We also have Dr. Chris Palestro with us. Dr. Palestro was a Phase 3 investigator, and is currently involved in the study of LeuTech for several different aspects of osteomyelitis.

Mathew Thakur is with us. Mathew is the inventor of this product, LeuTech, and has been involved in its development and characterization for about 11 years now. M.B. Khazaeli assisted us in the development of our HAMA assays and procedures. And Kathleen Madsen is our

statistician.

The agenda for the day will include a description of LeuTech properties, kit contents, and preparation by Dr. Smith; a review of equivocal appendicitis with respect to its current management, treatment dilemmas, diagnostic issues, imaging modalities. Dr. Kipper will then present the imaging techniques associated with our product, LeuTech. And then Dr. McElvany will review our clinical development program.

By way of a brief introduction, Palatin Technologies is a biopharmaceutical company founded in 1996. In addition to a number of research projects and research platforms that we're working on now, we have two products that are in development. P141 is a peptide for the treatment of erectile dysfunction. That is about to enter clinical trials. And then of course we have the LeuTech radio imaging agent, which will be the subject of our discussions today.

LeuTech is a murine IgM monoclonal antibody. It is specific to the CD-15 antigen found on the surface of human neutrophils; I might add only human neutrophils. When Dr. Thakur identified this antibody has having some clinical utility, he anticipated that it would act as a whole blood white blood cell imaging agent with broad application, and with potential applications and advantages relative to the

existing white blood cell agents. He anticipated that the in vivo labeling would give rise to a reduction in blood handling of course, and therefore faster results, and also the elimination of misadministration or reinjection errors.

Dr. Thakur started the development of this compound in 1989. The first human clinical use was in 1990, under a physician-sponsored IND. That IND addressed the possible use of this product in a number of different infections. It was a proof of concept study.

Palatin, as I say, got involved in 1996, and we submitted our IND in 1997. The initial indication that we chose to demonstrate this product's properties was appendicitis with equivocal signs and symptoms. We chose that particular indication because it occurs commonly, because we perceived a need for additional diagnostic information in that indication. And because this indication offers us a rapid and certain diagnosis in positive patients, and therefore allows for very high power in the study.

The biologic license application for this product was submitted in November of last year. About that time we commenced studies in additional indications, as you see here in several different aspects of osteomyelitis, post-surgical infection, and ulceratic colitis.

Today we are here talk about LeuTech for equivocal

appendicitis. The proposed indication for this product is scintigraphy with Tc 99m Anti-CD15 Antibody as indicated for the diagnosis of appendicitis in patients with equivocal signs and symptoms. And it is useful to rule out appendicitis in patients presenting with equivocal diagnostic evidence.

We hope by the end of our presentation to have demonstrated to you that LeuTech is accurate in patients presenting with equivocal signs and symptoms; that it is safe; and that it improves patient management.

Now I would like to turn the discussion over to Dr. Smith.

Agenda Item: Description of LeuTech - Terry Smith, Ph.D., Executive Director, Product Development, Palatin

DR. SMITH: Thank you, Charlie. Members of the committee, ladies and gentlemen, my task is to give you a brief description of the product which will be the subject of this discussion, and a few of the properties relevant to its application as an infection imaging agent.

As mentioned previously, LeuTech is a monoclonal antibody that binds to the CD-15 site on human neutrophils. It avidly binds to the antigen's own human neutrophils as indicated by the binding constance and the abundance of the binding sites. In addition, at the dosage that we use in

these studies, there is no effect on the function of the neutrophils, which includes chemotaxis, phagocytosis, and the adherence.

LeuTech is an IgM pentameric monoclonal antibody. It is produced in cell culture from an hybridoma cell line, with a molecular weight of approximately 970,000 Daltons. The distribution half life in blood is approximately 18 minutes, with an elimination half life of about 8 hours. Of the blood reactivity, approximately 14-50 percent of the blood radioactivity is associated with the neutrophil.

The kit itself is composed of lyophilized vial and an ampule of ascorbic acid. The lyophilized vial contains 250 micrograms of the monoclonal antibody, along with sufficient excipients required for the radiolabeling. The ascorbic acid is used for final make up to final volume.

The actual reconstitution of the product involves adding 20-40 mCi of Technetium to the lyophilized vial, followed by a 30 minute incubation at 37 degree celsius, and then dilution up to final volume with the ascorbic acid.

The labeling efficiency to typically than 90 percent by ITLC analysis. Over a large number of samples we actually have gotten in excess of 96 percent labeling efficiency.

At this time I would like to introduce Dr. Eric Rypins, who will discuss the equivocal appendicitis.

Agenda Item: Equivocal Appendicitis - Eric Rypins, M.D., Department of Surgery, Tri-City Medical Center

DR. RYPINS: Thank you, Terry. My job this morning is to discuss appendicitis, and in particular, equivocal appendicitis from a surgeon's perspective. I wanted to begin by showing you this data which was derived from CDC's review of all hospital discharges over a five year period. Appendicitis is the most common cause of abdominal pain that requires surgery. And excluding trauma, it's the most frequently encountered condition requiring emergency surgery in both adults and children.

There are 250,000 new cases of appendicitis every year, with a peak incidence that occurs in the second and three degree of life. A person's lifetime risk of having appendicitis is 7 percent, and it's approximately equal in males and females.

The negative laparotomy rates for appendicitis when the diagnosis is made correctly are still quoted as being between 12-30 percent, and it's higher in specific population groups where the diagnosis is more difficult to make. And those would be those patients who can't provide you with an adequate history, or where physical examination becomes more difficult.

The classical picture of appendicitis is one of the young person who arrives that emergency room with a

history of having had centralized abdominal pain, that over a period of time localized to the right lower quadrant. And is associated with the signs of anorexia, guarding, and leukocytosis typically.

Unfortunately for us as surgeons, about 50 percent of the patients who present to the emergency room with appendicitis actually have the classical picture, and the rest would present in a way that we would describe as being atypical or presenting with equivocal signs and symptoms.

An accurate and timely diagnosis in these patients is particularly difficult when: patients show up in the emergency room early in the course of the disease, before the full syndrome has had a chance to develop; in reproductive age females where there are other abdominal conditions affecting the right lower quadrant that make the diagnosis of appendicitis more difficult; in pregnant patients where the appendix is moved from its typical location in the lower abdomen by the gravid uterus; and at the extremes of age where the patients sometimes aren't able to give us an accurate history, and because the incidence of disease is lower in that particular group, it tends to be lower on the list of differential diagnoses.

So when the patient presents to the emergency room and has equivocal signs and symptoms, surgeons have traditionally had three choices as to what to do with these

patients. The surgeon's index of suspicion for appendicitis is relatively low. The patient appears to be relatively cooperative and understanding of the problem, he can be sent home. And that would be the wrong thing to do for patients with appendicitis.

Patients can go to immediate surgery. This would be the wrong thing to do obviously for patients who don't have appendicitis.

And typically, admission and observation is the course that is taken until the full presentation of the disease declares itself, and the patient's diagnosis becomes clearer. But this is never ideal in either case. Admission and observation is associated with unnecessary admission, which is costly, and unnecessary in patients who don't have appendicitis. And it delays the treatment and surgery for the patients that do have appendicitis.

So really in the appendicitis, the problem is unnecessary admission. And even worse is unnecessary surgery.

The problem for the patients with appendicitis is that the delay in the treatment of appendicitis can lead almost invariably to perforation and sepsis if the disease is not diagnosed in time. If patients are sent home in error, we found at our institutions and most others that they almost invariably return to the emergency room several

days later with a perforated appendix. And that when the patients present in the latter stages of the disease after the appendicitis has become complicated, there is increased morbidity, prolonged hospitalization, the need for costly antibiotics, and sometimes even death.

To assist us in dealing with these patients, there have been some recent improvements in the modalities that are used for assisting us with the diagnosis, and these include ultrasound and computer tomography, particularly the helical or spiral CT scan. And the ultrasound is a very highly operator-dependent modality. In those centers where there is an institutional expertise, excellent results can be achieved, but it really does vary quite a lot, depending on who is doing the ultrasound, and how experienced they are.

And in patients who have perforation of the appendix the sensitivity is particularly low because it depends upon an enlarged appendix to identify the patients with appendicitis. When the appendix perforates, it shrinks in size, and makes it more difficult to find. Most of the series that discuss ultrasound have found that in this particular population, the sensitivity rates are quite low.

Computer tomography, on the other hand, has been reported recently as having an extremely high accuracy, however, the optimal technique of how to do the helical CT

is quite variable amongst institutions, and includes the use of intravenous, oral contrast, contrast enemas, followed by CT, and the use of no contrast at all.

Use of intravenous contrast can sometimes be dangerous in patients with renal impairment. When patients receive oral contrast, and if the test is positive and have to go to the operating room, that will alter the anesthetic management of the patient such that the patient has to be treated as having a full stomach, because gastrograph and aspiration is a very serious complication for the anesthesiologist. If no contrast is used, then there is a question as to whether the CT scan will be as accurate.

In particular, contrast enemas also have been shown to have a high sensitivity and specificity in diagnosing the disease, but they are uncomfortable. They are unpleasant, and in particular radiologists complain that patients and technicians have to deal with a very young patient or a very elderly patient who can't the hold the contrast, and that kind of makes a mess.

So in conclusion, the management of appendicitis still remains a problem. The current modalities, as they exist, have promise, but they all have their limitations. We feel that LeuTech has the potential for improving the patient management in these difficult patients. And after an institutional experience personally with 98 patients at

my institution, myself and my colleagues have found that LeuTech is an extremely valuable tool for diagnosing equivocal appendicitis. It has assisted me and my patients at my institution in managing these difficult patients.

I'm going to call upon Dr. Kipper next as our nuclear medicine physician who will discuss the imaging use of LeuTech product. Thank you.

Agenda Item: Imaging Techniques & Interpretation - Samuel Kipper, M.D., Director, Nuclear Medicine, Tri-City Medical Center

DR. KIPPER: Thank you, Eric. As a nuclear medicine physician in a community hospital setting, I have had the opportunity to evaluate LeuTech in approximately 100 patients, as Eric has alluded to as part of Phase 2 and Phase 3 clinical trials. My role here today is to walk you through imaging techniques, image interpretation, show a few cases, maybe a handful of cases, and demonstrate in those cases were LeuTech has the ability to impact patient management.

The LeuTech imaging techniques were developed and refined during the Phase 2 trials, and implemented in the Phase 3 study for patients with equivocal signs and symptoms of suspected appendicitis. A few key points in patient preparation. First of all, there is no patient preparation required, which is a very nice for a nuclear medicine lab.

The patient is placed supine on an imaging table. The gamma camera is placed above the lower abdomen and pelvis, where the appendix anatomically would lie. Intravenous administration of the LeuTech is followed immediately or within a couple of minutes following the injection. Sedation was not required in any of the Phase 2 or Phase 3 patients, including adults and children.

On your right are two whole body scans obtained from a patient from the Phase 3 clinical trial. This happens to be a 14 year old male with suspected appendicitis, who has a negative scan. I show these whole body images just to orient you to the biodistribution of the product.

First of all, there is some blood pool activity -- there is LeuTech in the blood pool before clearance. Now clearance is rapid most of the time, but it be variable. So in some of the cases I'm going to show you, you are going to see some landmarks in the iliac vessels, and maybe even aortae and vena cava. There is very rapid uptake in the reticula endothelial system, as evidenced by liver uptake, spleen uptake, and bone marrow uptake.

There is also urinary excretion. The urinary route of excretion is the primary route of excretion for this product. And in all cases you will visualize kidneys and bladder. And we as nuclear medicine physicians have

developed techniques to work around the biodistribution. It's very important to empty the bladder prior to imaging, obtaining oblique views. And what we found on immediate andolate(?) imaging is that there no evidence of intestinal excretion or biliary excretion that may interfere with the interpretation of the images.

This is a typical planar view obtained 72 minutes following injection of LeuTech. This is a 15 year old male with suspected appendicitis who was negative. I show this to show you the appendicitis zone, which helps us in interpretation. What we found is that any LeuTech uptake within this appendicitis zone would be considered positive for appendicitis.

So reviewing approximately 56 cases in the Phase 2 clinical trials, and extrapolating to other imaging nuclear medicine studies for appendicitis, we came up for criteria for diagnosis of a positive scan for appendicitis. The primary indicator or criteria that we use is location of abnormal LeuTech uptake. That is basically any uptake of any intensity level, and any distribution within the appendicitis zone I just showed you.

We also rely on asymmetry. We would like to see uptake in the right lower quadrant greater than the left lower quadrant. And also another important finding would be the persistence of the abnormal LeuTech accumulation.

LeuTech accumulation within appendicitis does not disappear over time, and it does not disappear with positional maneuvers.

The criteria for a negative scan are quite simple. It's basically absence of abnormal LeuTech accumulation within the appendicitis zone within a period of imaging. Now the presence of abnormal LeuTech uptake outside of the appendicitis zone is positive for other intra-abdominal infections and inflammatory processes, however if there is uptake within the right lower quadrant appendicitis zone and outside the appendicitis zone, that scan would be interpreted as positive for appendicitis, with the potential for perforation.

As far as the imaging technique, following injection we start a dynamic series of acquisition sequences. This is the first acquisition sequence, which we call our dynamic acquisition is 40 minutes of imaging. We have 10 four minute frames, which we play back as an endless loop cine, which I will show you later when we go into the cases.

This demonstrates the clearance of blood pool activity, the renal excretion. And again, we're concentrating on this area, which is clear through the 40 minutes of imaging. This happens to be from an 8 year old female from the Phase 3 clinical trial.

Following the dynamic sequence, we have the patient get up and ambulate, void to try to empty the bladder as much as possible. And we obtain high count static images in multiple projections. In all studies we included anterior oblique imaging in order to offset a potential area of uptake in the appendix against the normal biodistribution in the blood vessels, or sometimes even in the bone marrow. As you can see, these images are extremely clear, with low background.

This is the first case I would like to show you. This is going to demonstrate the focal uptake pattern. This is one of the static images from the dynamic sequence. If we play this dynamic sequence, this will run us through the first 40 minutes of imaging, and this is basically how we interpret the studies. As you see as the image will play frame by frame, you can see the appendix showing up quite rapidly with high intensity.

Following voiding we obtain a high count planar image, as I mentioned before. I think on the next planar image you will be able to see the appendix. Again, focal uptake, right lower quadrant, asymmetrical. It persists throughout imaging. This is a typical positive case. This is a 43 year old female who presented with atypical signs and symptoms of appendicitis, and ended up having a perforated appendicitis.

This is another typical appendical pattern that we see on these types of scans, which is the linear uptake. This was a 17 year old male that presented with atypical signs and symptoms. And this patient went to surgery following the positive LeuTech scan, and had a long retrocecal appendix measuring 9 cm in length.

This next case is the diffuse pattern of uptake of LeuTech within the appendicitis zone. And if we start this dynamic sequence, we will see that there is abnormal uptake appearing immediate after injection, spreading out in the right lower quadrant, even extending out into the left lower quadrant somewhat. This was a 61 year old female, who at surgery had appendicitis with phlegmon, and lots of perioappendithal inflammation.

This next case is a 34 year old female presenting with atypical signs and symptoms of appendicitis. I show you this case only to show you the lower ends of the extreme of uptake of LeuTech. But still, clearly there is abnormal LeuTech accumulation, greater in the right than the left. An additional finding on this scan of a focal uptake in the right lower pelvis. This patient at surgery had perforated appendicitis with a drop abscess in the pelvis. So there is very good anatomical and image correlation in this study.

I would like to show a couple of cases now to illustrate the impact that LeuTech has on patient management

in patients from the Phase 3 clinical trial. This is a 26 year old female, who upon presentation, the surgery felt that without the availability of any other imaging tests, which was part of the protocol, that this surgeon would probably operate on this patient.

This patient was enrolled into the LeuTech clinical trial, had a negative scan for appendicitis. Management was altered. The patient was discharged home, and ended up not having any appendicitis. The abdominal pain resolved within a couple of days. This illustrates the potential for LeuTech to avoid unnecessary surgeries.

This case is 26 year old male, again presenting with atypical signs and symptoms of appendicitis. Without the benefit of having other imaging studies available to this surgeon, this surgeon felt that the patient could probably be sent home with careful follow-up. The patient was enrolled into the clinical trials. The LeuTech scan was positive for appendicitis. This is a four minute image, four minutes after injection. We see the appendicitis; 20 minutes. At 40 minutes it becomes more clear after the clearance of the blood collectivity.

The patient went to surgery. The surgeon reported evidence of a normal appearing appendix, but there was mesenteric adenopathy. I went to the pathology lab, retrieved the specimen, put the appendix under the gamma

camera next to the lymph nodes, and there was radioactivity in the appendix. The pathology report came back, appendicitis and reactive nodal hyperplasia.

A couple of points here. There is a management point here in that LeuTech has the ability to avoid sending a patient home with appendicitis. So this is a reverse management case. The other point here is that LeuTech, since it's a physiologic imaging agent, has the potential to diagnose appendicitis or other infections earlier than the appearance of morphologic changes.

This last case happens to be a false positive case for appendicitis. This patient was a 34 year old male presenting with atypical right lower quadrant pain. And in this study there is a focal uptake just above the bladder. There is some low grade right lower quadrant uptake. And this was interpreted as positive for appendicitis.

This patient went to surgery and ended up having Crohn's disease of the terminal ileum with obstruction. So this demonstrates that we do have false positive studies with LeuTech, but the white cells will go through other areas of inflammation. It's a false positive for appendicitis, but it's actually a true positive for surgical disease.

In my experience as a nuclear medicine physician, I would like to sum up my experience with LeuTech. Our

overall experience at our center has been extremely favorable. We have found that this test is very simple to perform by nuclear medicine standards. It is safe. It does not require blood handling, therefore it lowers the risk of passing on infections such as HIV and hepatitis.

These images for nuclear medicine standards are very easy to interpret. This test clinically provides very rapid and diagnostic results in what I might is a difficult group of patients with equivocal presentation of appendicitis. Overall, at our institution we found that this product has improved patient management.

To date, I still have the surgeons in our institution and the emergency room, I might add, still requesting the fast nuclear medicine scan, which is the LeuTech. So in summary, this is a product that would be very beneficial to add to the nuclear medicine community.

Next I would like to turn the podium over to Dr. McElvany, who would like to review the clinical results.

Agenda Item: Clinical Development Program - Karen McElvany, Ph.D., Director, Clinical Affairs, Certus International Inc.

DR. MC ELVANY: Thank you, Sam. My purpose this morning is to provide a brief summary of the LeuTech clinical program. As outlined here, we have studied a total 439 subjects with LeuTech, subjects in the Phase 1, 2, and 3

studies that Palatin carried out, in addition some preliminary work on their physician's IND, as well as some work done in Europe. And then more recent work done on the osteomyelitis IND on looking at efficacy in osteomyelitis, and a repeat dose HAMA study.

The Phase 1 study was performed in 10 healthy, normal volunteers to evaluate safety, biodistribution, and calculate radiation dosimetry. We had no adverse events reported, and no clinically significant changes in vital signs or clinical laboratory measurements that were related to LeuTech.

The radioactivity was excreted primarily in the urine. And at one hour after injection, most of the radioactivity, or 45 percent was present in the liver. We used the biodistribution data to calculate radiation dosimetry, and the target organs are outlined here -- the spleen, liver, kidneys, and bladder -- with an effective dose equivalent of 0.068 rem/mCi. These radiation doses are comparable to those of other nuclear medicine procedures, and are also quite comparable to those for abdominal CT.

Our Phase 2 and Phase 3 appendicitis studies were carried out in patients presenting with equivocal signs and symptoms of appendicitis. The Phase 2 study was carried out in 56 patients at 2 centers in the United States. In this study our gold standard for comparison of the LeuTech

diagnosis was the final institutional diagnosis, which was based on surgery/pathology results in patients who underwent surgery, or in one month clinical follow-up in patients who did not undergo surgery.

The Phase 3 pivotal study was very similar in design to the Phase 2 study. It was carried out in 203 patients at 10 centers in the U.S., and again the gold standard was the final institutional diagnosis, surgery results, or in cases that didn't go to surgery, 2 week clinical follow-up.

Inclusion criteria were very similar for both studies, males and females of all age groups. In the Phase 2 study our lower age limit was 8 years, which was put down to 5 years for the Phase 3 study. All patients presented with right lower quadrant pain and equivocal presentation of acute appendicitis as assessed by the referring surgeon based on the absence of typical signs, symptoms or history.

Patients were presented with one or more of the list of equivocal signs and symptoms shown here: atypical history of symptoms; atypical physical exam; temperature less than 101 degree; or a white blood cell count of less than 10,500. In fact, the vast majority of our patients had more than one of these equivocal signs and symptoms.

Major exclusion for the studies were also quite similar. Pregnancy and nursing women were excluded from

both studies. And in addition, in Phase 3 we excluded a known diagnosis of pelvic inflammatory disease. We also excluded patients with two or more hospital admissions for abdominal pain within the preceding six months that was unresolved, and patients who had already undergone CT for the work-up of their current episode of abdominal pain.

The Phase 3 clinical trial design was based on primary efficacy indicators of sensitivity and specificity of the blinded readers' evaluations. And the statistical evaluation was performed using a 95 percent one-sided confidence interval.

Secondary efficacy indicators included the accuracy, positive and negative predictive values of the blinded readers' evaluations, as well as all of the efficacy evaluations for the site investigations. We also looked at intended clinical management, and likelihood of appendicitis as assessed by the referring physicians.

Dosage of LeuTech was the same for both studies, the adult dose 10-20 mCi of Technetium containing 75-125 microgram of antibody. In pediatric patients we scaled the dose on a body weight basis as 0.21 mCi per kilogram of body weight, with a maximum of 20 mCi in a large child.

Image acquisition has already been gone over by Dr. Kipper. Simple planar imaging, dynamic images, followed by a series of static planar images. We permitted in the

protocol any additional imaging or SPECT imaging at the discretion of the investigator.

The images we obtained in the Phase 2 and Phase 3 studies were read by the site investigators, and also by blinded readers. All readers read the images as either positive or negative for infection, and we permitted no indeterminate reads. Images that were classified as positive for infection were then further classified as either appendicitis or other infection. And in Phase 3 we also asked the readers to indicate the time the image first became positive.

Our blinded reads were managed by an independent core laboratory. We had three blinded readers who were otherwise participating in the study or associated with any of the sites, and the readers read the images independently.

The readers were presented with no clinical history of symptoms in Phase 3, however, in Phase 2 we did provide the reader with the equivocal signs and symptoms that were checked on the entry criteria. Readers did get general demographic information, and they were provided the images on computer monitors, as were the site investigators, and permitted to look at the dynamic images as endless loop cine displays.

We also looked at patient management plans in these studies. We asked the referring surgeons to complete

a questionnaire prior to the LeuTech imaging indicating first of all, the likelihood of appendicitis based on a five point scale, and also their intended treatment plan, choosing between surgery, admit for clinical observation, or send home. We then asked the surgeons to complete the same questionnaire following review of the LeuTech imaging results, but prior to any further testing or treatment of the patients.

Now onto some results of our studies. In Phase 2 we enrolled 56 patients, ranging in age from 9-77 years, with 15 patients in the pediatric age group. We had a 50-50 split in patients that had appendicitis, and did not have appendicitis. Of the 28 patients with appendicitis, 9 had perforated appendix. And of the 28 without appendicitis, we noted 7 other infections.

Efficacy results are presented here for the Phase 2 study. For the blinded readers the aggregate read for the three readers, and also for the site investigators. You can see the results are quite encouraging, with high accuracy and sensitivity for both the blinded readers and the site investigator, and the data provided a basis for the design of our Phase 3 trial.

In Phase 3 we enrolled 203 patients at 10 sites, giving 200 evaluable patients. We had 2 patients who were lost to follow-up, and 1 positive patient who went to

surgery prior to completion of the required minimum of 30 minutes of imaging.

We had fairly even good distribution of enrollment among the 10 sites, with 6 sites enrolling between 19 and 39 patients. Our age range here was 5-86 years, with 49 patients in the pediatric age group. And our split between appendicitis and not appendicitis, we had 59 or 30 percent patients with acute appendicitis, 13 of them perforated, and 141 or 70 percent of the patients presenting with a final diagnosis of no appendicitis, and within that group, 23 other infections were noted.

We designed our protocol to enroll patients with equivocal signs and symptoms of appendicitis based on the absence of the classical signs and symptoms of design. However, to evaluate whether we had a truly equivocal population, we then looked at the distribution of surgeon's estimates of likelihood of appendicitis on their pre-scan questionnaire, as well as the prevalence of their choice of admit for observation as an intended clinical management plan.

This graph shows the distribution of the number of equivocal signs and symptoms that the patients presented with for the Phase 3 trial. You can see that 92 percent of the patients enrolled with 2 or more equivocal signs and symptoms, and approximately two-thirds enrolled with 3 or

more equivocal signs and symptoms.

Looking at the likelihood of appendicitis as assessed by the surgeons prior to the LeuTech study, you can see that 85 percent of the patients fall into the middle of the spectrum here, in the 20-79 percent likelihood range of appendicitis.

And lastly, if you look at the pre-scan intended clinical management assessed by their surgeons, 60 percent of the patients planned for admit for further observation, cases where the surgeon was not willing to make a decision to go to immediate surgery, or feel comfortable sending the patient home.

The age distribution of the patients in our Phase 3 are presented here. Again, we had 49 patients in the pediatric age range, 10 geriatric patients, and the remainder in the adult age group.

Again, LeuTech imaging was just simple planar imaging. SPECT was not required, and it was optional, as I mentioned, in the protocol. In fact, in our 203 patients, we only had 9 patients who underwent SPECT, 8 of those being at a single site. And we did not include the SPECT images in our blinded reads.

Time to first positive image is actually quite fast with LeuTech, permitting our fairly rapid diagnosis of disease. As shown in this graph, 50 percent of the patients

had a positive image within the first 5 minutes of injections of LeuTech, and greater than 90 percent were positive within 50 minutes after injection.

Efficacy results for the Phase 3 study are outlined here. Again, these are the aggregate reads for the three blinded readers. And I would like to point out that we had quite high concordance between the pairs of readers, with concordance rates ranging between 88-90 percent.

You will note that for the site investigators, the numbers are somewhat lower. That's because the first two patients at each site at other than Dr. Kipper's site, which was the lead site, were excluded from this analysis, because they were considered training cases where the investigator was permitted to review their interpretation with Dr. Kipper.

I would like to point out the high accuracy for LeuTech that was quite similar between the site investigators and the blinded readers; 88 percent for the blinded readers, 87 percent for the site investigators. A sensitivity of 75 percent for the blinded readers, 91 percent for the site investigators. And corresponding specificity of 93 percent for the blinded readers, and 86 percent for the site investigators.

I would especially like to point out the high negative predictive values of 90 percent for the blinded

readers, and 96 percent for the site investigators.

We also calculated likelihood ratios for the efficacy data for our Phase 3 as presented here. We found that the odds that an investigator would correctly diagnose appendicitis with the LeuTech were 6-13 times greater than the pre-test odds of appendicitis. And likewise, we found that the odds that an investigator would miss a diagnosis with LeuTech was reduced one-ninth to one-third times the pre-test odds.

This slide compares the blinded review results for both the Phase 2 and the Phase 3 studies, which you can see are quite comparable, but actually somewhat higher for the Phase 3 study. And then this slide compares the site investigator results for the two studies. Again, the accuracy was essentially equal for both studies, and the very high negative predictive value of 96 percent for both of the studies.

Looking at some of the patient management data, this shows the surgeons' estimates of likelihood of appendicitis before and after the LeuTech scan. This is in patients with appendicitis.

ROC curves were generated to compare the surgeons' estimates of likelihood of appendicitis before and after the scans. And we saw a definite improvement after the scans, with the area under the curve increasing from 0.81 to 0.95.

The difference between these two curves, which is assessed by comparing the areas under the curves was significant, with a P less than 0.0001.

In comparing intended clinical management as assessed by the surgeon in patients with appendicitis, you can see here that we had three patients who shifted from a plan of send home prior to the scan, to a plan of appropriate surgery following the scan. We also had 25 patients who shifted from the admit and observe plan, to a plan for immediate surgery.

I would like to note that 1 of the 2 patients for whom send home was still a plan after the scan in fact had a positive LeuTech scan.

Looking at the intended clinical management differences for patients without appendicitis, it is important to note that roughly half of the patients who were to be admitted for observation prior to the scan shifted to an appropriate plan of send home after the scan.

There were approximately equal numbers of patients planned for surgery before and after the scan, but these were not the same individual patients. And in fact 4 of the 13 patients post-scan who were planned for surgery, actually required surgery for other conditions.

In summary of the clinical management data, we found a definite favorable impact of LeuTech on the

management of our patients; 74 of 189 patients, or approximately 39 percent we found favorable shifts. Some of the key ones are outlined here; 25 patients with appendicitis shifted from a plan to admit for observation, to a plan of immediate surgery. We had no patients with appendicitis shift away from the appropriate plan of surgery. And we have 39 patients without appendicitis who shifted from an admit and observe plan, to send home. And the different between these pre- and post-scan management data was highly statistically significant.

I would like to now briefly summarize the overall safety for our LeuTech database. Our safety measurements included: adverse events, clinical laboratory measurements, vital signs, and assays for Human Anti-Mouse Antibody, or HAMA formation. The overall summary of safety is provided for 439 subjects. This includes all subjects in the Palatin INDs and in other studies; 393 of these subjects were included in the BLA filing. An additional 46 subjects were summarized in our 120 day safety update to the BLA.

We had 202 males and 237 females in these patients, with a mean age of 34 years, age range from 5-91. The mean antibody does in this group in our total population was 120 micrograms, with a mean radioactive dose of 14.5 mCi.

Age distribution is shown here. In this total

population we had 66 pediatric patients, 30 geriatric patients, and 343 patients in the 18-64 year age range.

Overall incidence of adverse events in this population, we had 30 of the 439 subjects experience a total of 39 adverse events. None of these were serious, and all were classified as mild or moderate in intensity, except for a single moderate to severe case of injection site pain.

The overall incidence of adverse events is presented here using the Costart(?) Standard Dictionary terminology. The most commonly observed adverse event was vasodilatation, which in fact was reported as flushing or hot flashes by the investigators on the case report form. This was reported in 11 subjects or 2.5 percent. It was a relatively transient effect that resolved without intervention, and in no cases was associated with any hypotension. We observed dyspnea in 4 patients, or 0.9 percent of the total population, and all other adverse events in less than 0.7 percent of the patients.

Adverse events that were classified by the investigators as possibly or probably related to LeuTech are outlined here. That included 20 adverse events in 14 subjects. And again, the only adverse event that was of a percentage greater than 1 percent was the vasodilatation or flushing in the 11 patients.

Clinical laboratory measurements were obtained in

4 of our clinical trials in a total of 242 subjects. Investigators were asked to assess clinical significance of any laboratory changes, and they noted 7 clinically significant changes in 4 subjects, or 1.7 percent of our population. These were classified as a lab error in one case, related to patients' underlying disease in two cases. And there was only a single case that it was impossible to rule out any possible effect with LeuTech, and this was some elevated liver enzyme in a patient that resolved spontaneously without any intervention.

Vital signs were measured in six of our trials in a total population of 383 patients, including pulse rate, blood pressures, and oral body temperature. We looked at mean vital sign changes from baseline and noted several statistically significant changes, however, all of these changes were very small in magnitude, and of no clinical relevance.

The protocol-defined clinically significant changes in vital signs is outlined here: systolic blood pressure changes greater than 35 millimeters; diastolic greater than 25 millimeters; or pulse rate changes greater than 20 beats per minute. Clinically significant changes according to these criteria were noted in 20 subjects, changes in pulse rate in 12 subjects, and changes in blood pressure in 8 subjects. And in no cases were these vital

sign changes attributed to LeuTech.

We also looked at HAMA response following injection of LeuTech. This evaluated in three studies in a total of 54 subjects. It has included a 30 subject normal volunteer study specifically designed to look at HAMA response. Also we recorded HAMA measurements in 20 patients in the Phase 3 appendicitis trial at FDA's request. And there 4 patients in the early investigator IND work that also underwent HAMA measurements. HAMA levels were measured at baseline, and at 3-4 weeks after injection in all of these studies, and no positive responses were noted in any of the subjects.

In summary then, we found that LeuTech is effective in two clinical trials for diagnosing and ruling out appendicitis. The results of our pivotal Phase 3 trial corroborated the earlier Phase 2 results. The accuracy of blinded readers of 83-89 percent was quite consistent with that of the site investigators at 87 percent. And we also found that the LeuTech scan had a favorable impact on intended clinical management.

LeuTech we found to have an excellent safety profile, with no serious side effects. We had only 30 of 439 subjects experiencing any adverse events. None of these were serious, and 20 AEs in 14 subjects were considered possibly or probably related to LeuTech. Flushing was

reported by 11 patients, or 2.5 percent of our population, and no other adverse events had incidences over 1 percent. We also noted a minimal incidence of clinically significance changes in vital signs or clinical laboratory measures, and no HAMA response following a single injection.

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

Now I would like to turn the podium back over to Mr. Putnam.

Agenda Item: Conclusion - Charles Putnam, Chief Operating Officer, Palatin

MR. PUTNAM: Thank you, Karen.

I'm supposed to present our conclusions, which I would think would be evident by now. We, the sponsor, have concluded that LeuTech, in the hands of investigators, is accurate in the patient population studied. It was useful to rule out appendicitis with a negative predictive value of 96 percent. The safety profile was excellent. The product appears to be safe.

And we conclude that it improves patient management, allowing clinicians to accelerate surgery in patients who require it, and to safely discharge patients who do not. Therefore, we believe that the data we have

presented supports the indication which we propose.

Perhaps this would a good time now to take questions if there is any clarification required. No questions? Thank you.

DR. PONTO: Are there any clarification questions from the committee at this point in time?

DR. HOOVER: [Question off mike.]

MR. PUTNAM: Dr. Kipper, would you address that question, please?

DR. KIPPER: The routine sequence of imaging included a 40 minute dynamic imaging sequence where the patient is lying comfortably supine on an imaging table. Following that 40 minutes, the patient gets off the table, ambulates, is asked to void, and returns for a set of high count planar images on the same imaging table, which take about 20 minutes. And if any additional images are required, that's up to the discretion of the investigator.

DR. HOOVER: You can diagnose 50 percent appendicitis in the first 4 minutes, 90 percent at the 50 minute scan. So what is the average patient going to have to go through to get to that point?

DR. KIPPER: The protocol requires that the patient complete the first 40 minute dynamic imaging sequence, and the whole set of planar imaging sequence. By that time we are roughly 70, 80, 90 minutes. If you

remember that curve -- if you could bring up that curve again on the first positive. In 90 percent of patients the appendicitis will show up by 48 minutes. And we pick up the other 10 percent generally within 90 minutes.

We feel pretty comfortable that if the scan is unequivocally negative after the first dynamic sequence, and after the first set of planar images generally at 90 minutes, that we feel comfortable stopping the imaging procedure and calling it negative. So you will get your answer in 70-90 minutes; sometimes sooner if it's unequivocally positive.

DR. WHALEN: A follow-up question while Dr. Kipper is still there. Perhaps he might be best to answer it. We are talking then time from injection. But the more pragmatic question would be from time of decision, or I guess better put, from time of non-decision of appendicitis to time of interpretation of test in patient, decision-making as to go into OR or not, what is the cumulative time there?

DR. KIPPER: Well, it depends on if it's during the night or during the day. At night you have to call in the nuclear medicine technician. But assuming the nuclear medicine technician is in the department, the ER calls us, from that time it would take about a half hour to prepare the product, and about on the average I think it was 80

minutes to perform the scan. So that would be the average.

In some cases you could stop earlier, and in very few cases would you go beyond that. Does that give you a rough idea? So I would say on the average, 80 plus 30.

DR. WHALEN: Yes, that does, thank you. A second question that might best be Dr. Freiberg(?), but you can decide after I ask it. The gold standard was the institutional diagnosis, which I assume is going to be highly keyed upon the pathologic report. Over the last five years if our computer system is anywhere near right, of 107 appendices that I have taken out, I had 3 that I would have been convinced were normal at the time of surgery, but due to what I consider pathologic beneficence, were read as acute appendicitis.

Was there an attempt to look at post-operative diagnosis written in the brief post-operative note versus pathologic report, and if so, was there a discordancy?

DR. MC ELVANY: We did look at both surgery report and pathology report. And we took the pathology report as being the gold standard if there was a discrepancy. And I think we only had one or two cases where there was a discrepancy. There were a couple of cases where the surgeon thought the appendix looked normal, but the pathology report was early appendicitis.

DR. TULCHINSKY: I noticed that there has been

some drop in neutrophils and leukocyte count. Were any of the patients studied, neutropenic by any chance?

DR. MC ELVANY: No, we studied no neutropenic patients at all. The lowest white blood cell count I believe was approximately 4,000 in the patient population that we studied.

DR. TULCHINSKY: That was by chance? It was not by exclusion?

DR. MC ELVANY: It was not by exclusion. I think it was probably by the fact that patients with appendicitis are not likely to --

DR. TULCHINSKY: Unless they are off the chemotherapy or something like that.

DR. MC ELVANY: Right.

DR. AMENDOLA: When the studies are done at night, the studies are read by the nuclear medicine physician at home or come to the hospital? How is that done?

DR. KIPPER: Right. In our department, we are far enough from a centralized radiopharmacy that we have what you call a hot lab. We label all of our products. So day or night the technologist comes in and prepares this kit. Now for labeled white cells it would take two hours to prepare, including drawing the blood, spinning down the blood, separating the white cells.

But with product it's a simple formulation that

any nuclear medicine technologist, any nuclear medicine department could perform, and it takes about a half hour to perform. And the product has a very long shelf life, so any nuclear medicine department could stock this product.

DR. AMENDOLA: In the interpretation of the study is done --

DR. KIPPER: Immediately. Are you talking about interpretation at night? Yes. I think most radiology and nuclear medicine departments now have teleradiology systems. And with our teleradiology systems, basically we are interpreting these scans the exact same way we would interpret them in the hospital, and that's basically on the computer, where you can could adjust contrast, and look at the endless loop cine.

DR. AMENDOLA: And those are certified?

DR. KIPPER: They are certified.

DR. PONTO: Are there any other questions from the committee for points of clarification only at this point? Not discussion points, just clarification.

DR. BLUMENSTEIN: I'm still interested in the outcome measure here of diagnosis of appendicitis. And there 39 patients that were classified as not having acute appendicitis by your primary diagnostic classification, who were by the pre-scan, classified as admit for observation, but post-scan were sent home, or the recommendation was send

home.

Suppose one of those patients went home and subsequently developed an acute appendicitis perforation and so forth. What happened? How does that patient show up in these tables?

DR. MC ELVANY: We actually did track the follow-up in all of our patients, and we had no patients that went home, and then first presented back with appendicitis. I believe I have a back-up slide that I could put up there, slide 115. We had six patients who had false negative LeuTech scans, and none of them were actually sent home. They all went to appendectomy, most of them on the same day, one, two days later. So we had no one that was sent home, and presented back to the hospital with appendicitis.

DR. BLUMENSTEIN: Well, what I'm interested in, are these patients then in the analyses classified as positive for appendicitis?

DR. MC ELVANY: Their final diagnosis is positive for appendicitis.

DR. BLUMENSTEIN: And no patient who went home --

DR. MC ELVANY: Presented back with appendicitis, correct.

DR. HOOVER: This is a follow-up question about the imaging. I guess I'm concerned about an 8 year old kids who is asked to be still on a table for 90 minutes, or 50

minutes, and then you're going to let them get up and move around, and then do the completion films. And you don't sedate these kids, is that correct? Because sedation makes it difficult for us to then do subsequent abdominal evaluation.

I guess my question is, is it necessary for the kid to be still to exclude bias and reasonably interpret the study?

DR. KIPPER: It's very helpful to have that child keep still to interpret the image, but from what I understand there were no images in the clinical trials that were evaluated by the blinded readers or the site readers that felt that any movement artifact hindered the interpretation of the study. Actually, I would say that most of the children held pretty still. They had their parents with them. They were actually quite cooperative.

And correct, sedation was not required.

DR. AMENDOLA: You don't have to be still?

DR. KIPPER: You do not have to be still for the full 90 minutes. It's basically for the first 40 minutes of imaging. And then we give them a break. When they come back for imaging, we have about another 20 minutes of imaging, but there are 5 images in that sequence, and the image takes about 2-3 minutes. So they can have a break in between those. So the longest time they hold still is 40

minutes.

DR. TULCHINSKY: In reference to chemistry and formulation, I have a question. I see that after incubation the volume is brought up to the desired by using ascorbic acid. Is there a particular reason for that? It's not routine for us to keep that, for example, in the radiopharmacy. Is normal saline just as good? Could I have a comment on that, please?

DR. SMITH: The ascorbic acid serves a two-fold purpose. First all, to dilute the preparation up to a workable, easily handed volume for injection. The second purpose is it does serve a stabilizer during the shelf life of the reconstituted material.

DR. TULCHINSKY: As a quick follow-up, how long and what would be the difference if one were to reconstitute the volume with normal saline?

DR. SMITH: I don't have that data. We have typically reconstituted with ascorbic acid both in our laboratory studies, and throughout the material that was used in the clinic.

MR. PUTNAM: May I just add that the ascorbic acid that is necessary for reconstituting the LeuTech is included in the LeuTech kit.

DR. PONTO: We are trying to limit the questions right now to just clarification from the sponsor. Dr.

Abramson.

DR. ABRAMSON: This is a follow-up question. Many of my patients are severely neutropenic, and the question of appendicitis is a very serious one. How would this product be used in those patients? Is it possible to use it in these patients?

DR. MC ELVANY: Since we haven't studied it in any patients that are neutropenic, we don't really have an answer. We don't have any reason to believe it wouldn't work, but we don't have any data to tell you that it does work.

This is a summary of the white blood cell counts of presenting patients. There were between 4,000 and 11,700, and no one presenting with clinical neutropenia. We had 5 patients who did have white blood cell counts below their institution's lower level, but not clinically neutropenic, all negative cases, and we were able to get good images. But we didn't have any positive cases in that patient population.

DR. KIPPER: I just have one comment, which would basically compare LeuTech to labeled white blood cell imaging. And this would incorporate broad infection imaging and appendicitis. With our existing techniques in nuclear medicine infection scan is performed by labeling white blood cells. If there are not enough white blood cells to label,

we cannot perform that technique.

So in a child which you have suggested having a scan, the existing technique, we would not be able to perform with a white count below 3,000 say. With LeuTech -- now I don't know this for sure -- it could be used in that patient, but theoretically LeuTech labels white cell neutrophil already at the site of infection. In a neutropenic patient, if there are neutrophils at the site of infection, it is basically independent of circulating neutrophil level. So we would anticipate that in neutropenic patients, that this might be able to be used.

DR. ABRAMSON: A follow-up question. The radiation dose of this study compared to radiation dose for CTs?

DR. MC ELVANY: I compared the doses that we had for LeuTech dosimetry, here shown 4.6 effective dose equivalent, and 6.9 in milliciverts(?) to some literature values for abdominal CT, and you can see they are fairly comparable in the two age ranges, less than 10 years, and 11-18 years.

DR. LINKS: A quick clarification on the fraction of the blood radioactivity that is associated with neutrophils. That number was 14-50 percent. I'm assuming that in the case of the lower end there, what "saves" you is the rapid blood clearance of the radioactivity that is not

associated with neutrophils. Is that right, or not?

In other words, you had a very nice target to background ratio. If I said, heck, I only have 14 percent of the blood radioactivity associated with neutrophils, that wouldn't necessarily be a good message. So it must be that you have relatively rapid clearance of the activity not associated with the neutrophils relative to that associated with the neutrophils.

DR. SMITH: That is a reasonable explanation for the reason. In addition to that, remember that only a fraction of the labeled neutrophils are required to be localized in an area of infection, but it is a very reasonable hypothesis.

DR. HAMMES: A formulation question again. As a nuclear pharmacist, I can say if we have to incubate something 30 minutes at 37 degrees C, we aren't going to get a dose out in 30 minutes. It's going to be more like an hour in the alutogenerator(?), and then incubated after you make it, and then do the QC, and then dispense it and do your documentation, and put it out.

But a bigger question is how critical is that 37 degrees C, and what kind of variation is acceptable? In my lab it takes us an hour or more to equilibrate a heating block for water bath from room temperature to 37 degrees C.

DR. SMITH: We have found that typically there is

a considerable improvement, or a considerable leeway built into the 30 minutes, however, we have recommended that as an approach forward. We typically have supplied heat-a-blocks. And for example, those get up to temperature at 40 degrees C in about 4 minutes. And we have done a study, which I don't have a slide for here, where we have looked at the labeling over time. There is probably for example, on a conservative basis, a plus or minus 5 minutes built into that time, and plus or minus 2 degree built into the temperature range.

DR. PONTO: Does that conclude all the questions for clarification from the committee? At this point in time if the agency is ready to proceed, we will go ahead with the agency's presentation.

Agenda Item: FDA Presentation: Products Review - Chana Fuchs

DR. FUCHS: Good morning. I will start with a very brief introduction of the product, and then Drs. Martynec and Lindblad will continue with the clinical part of this presentation.

This first slide introduces the review team working on this license application.

The product LeuTech is a kit for preparation of Technetium labeled RB5 anti-CD15 monoclonal antibody intended for IV administration after reconstitution and radiolabeling. Each kit contains one reagent vial with 0.25

mg of lyophilized, partially reduced RT5 murine IgM antibody and excipients, and 2 mL ampule of ascorbic acid for injection to be used as a diluent.

Now this is the proposed indication directly from the BLA. "LeuTech is indicated for the diagnosis of appendicitis in patients with equivocal signs and symptoms. It is useful to rule out appendicitis in patients presenting with equivocal diagnostic evidence."

The monoclonal antibody, RB5 anti-CD15 is a murine IgM. This is a cartoon of a partially reduced, labeled IgM. IgMs are pentameres. They therefore contain ten sites for interaction with the target antigen. RB5 IgM is partially reduced to all it to complex with the Technetium label. And the reduction process releases free cell hydrase for reaction with the Technetium and formation of the radiolabeled Tech antibody complex.

Now this is just one example of a partially reduced and labeled IgM antibody. There are many other sites in the molecule which can be reduced during the partial reduction reaction. And additionally, I'm only showing for ease of presentation, two Technetium molecules complex to this IgM, but a larger number of Technetium molecules may actually be binding. Now if licensed, RB5 anti-CD15 would be the first IgM to be licensed for use in patients.

The target antigen to which this monoclonal antibody binds is CD15. Now this is a branched oligosaccharide known as Lacto-N-neo-fucopentaose III that can be found on glycoplipids and glycoproteins expressed on the cell membrane. Now this carbohydrate structure defines the CD15 family of antigens. CD15 is an adhesive carbohydrate moiety that can bind to itself, as well as to other carbohydrates. It is important in cell-cell recognition, migration, and in mediating fibrocytosis of geocytal(?) activity, and hemotoxsis.

CD15 is reported to be strongly expressed by neutrophils, eosinophils, monocytes, and normal myeloid precursor cells. Activated T cells and Reed-Sternberg cells also have been reported to express CD15.

Now in the literature information on CD15 can also be found under these names, and all of these refer to a carbohydrate antigen in which the immuno-dominant structure is the oligosaccharide I showed you in the previous slide.

The rationale for using this antibody to assist in diagnosing equivocal appendicitis is that appendicitis is associated with a neutrophilic infiltration of the muscularis, and also usually the appendix mucosa. Now the Technetium-labeled RB5 IgM antibody binds the CD15 epitomes on the neutrophils found at site of infection or inflammation, allowing imaging of these sites.

Manufacturing of this monoclonal antibody occurs at a number of sites. Palatin, the sponsor of the BLA is responsible for and controls all steps in the manufacturing process, performs QC release testing, and manufacturing and filling are done by contract manufacturers. One contract manufacturer makes the IgM drug substance, while a second one manufactures and prepares the final drug product.

Now currently there are a number of significant outstanding manufacturing issues which still remain to be resolved. Dr. Martynec will now continue with this presentation.

Agenda Item: Nuclear Medicine - Lydia Martynec

DR. MARTYNEC: I will present primarily on the imaging aspect of the application, and Dr. Lindblad will follow with the clinical portion.

The primary clinical trials on the LeuTech product consisted of two trials, the 98004 trial, which enrolled 203 patients. That's the Phase 3 trial, in an open label design trial. And the supportive Phase 2 trial, 97003, which enrolled 56 patients, was also an open label design. Dr. Lindblad will discuss these in greater detail.

As far as the LeuTech imaging agent, the ghost of antibody itself was 75-125 micrograms. The radiolabeled dose for the standard adult, the dose was 10-20 mCi of Technetium 99m radiolabel. The sponsor considered the

pediatric age group as less than 17 years old, and that dose was then scaled down to 0.21 mCi per kilo, up to a maximum of 20 mCi.

The imaging protocol was standardized across all sites, with a total image acquisition of approximately 90 minutes. It consisted of two phases, the dynamic phase and the static phase. The immediate dynamic acquisition phase selected 10 sequential image frames at 4 minutes each. Then the patient ambulated for 10-15 minutes, voided. And then static planar images were collected. There were 5 static planar images collected: the supine anterior view, a supine posterior view, a right anterior oblique, and a left anterior oblique both collected at a 25 degree angle, and then lastly a standing anterior image view.

Image acquisition was standardized so that the anterior image was collected for 1 million counts, and then all subsequent images were collected for the same period of time. SPECT images were not performed routinely as part of the protocol.

As far as the blinded reading protocol, as in our guidance document, a blinded reading was performed by three independent blinded readers. But independent readers, I mean that they were not participating in the Phase 3 development program. Reading was scored per each reader, Reader 1, 2, and 3, and also an aggregate read was performed

where the majority ruled, two out of three results.

The blinded readers were provided with demographic information only, i.e., age, sex, height, and weight of the patient, but no specific patient information was given. The image sets were randomized. That is, the independent contractor presented the images on a database in a randomized fashion in standard format on the computer database.

And an independent evaluation was carried out. That is, independent, meaning that the images were read independently by each blinded reader in a separate room, and then the results were locked. And the results were recorded on an electronic case report form that essentially the same as the Phase 3 case report form that was in hard copy.

The blinded image evaluation report was essentially as I mentioned, the same as the case reports on one hard copy, and it recorded results of the image uptake regarding abnormal uptakes seen, negative or positive. If there was an abnormal uptake seen, the imager then recorded the uptake pattern, and the location of uptake in the so-called appendicitis zone, which Dr. Kipper actually showed previously. And the intensity of uptake, whether that uptake was low, moderate, or high.

The blinded image evaluation report further recorded the time that the scan became positive, that is the

minutes into the study that the image became positive; whether the uptake persisted throughout the study, denoted as yes/no; the technical quality was noted; and then finally, the LeuTech diagnosed was denoted as negative or positive. If there was a positive diagnosis, it was further classified as acute appendicitis or other infection.

As far as the reader training, training was given to both the Phase 3 investigators and the blinded readers. It was the same training program, submitted prospectively. It utilized eight cases from the Phase 2 trial, with a presentation of six positive cases and two negative cases. It specified criteria for image interpretation, and discussed some image pitfalls in the interpretation appendicitis.

Following this practice orientation session, the readers then did a practice blinded reading independently of 15 Phase 2 cases. And following that, the results in their image interpretation after their scoring took place was jointly reviewed with Dr. Kipper.

I'm quoting from the training manual from the sponsor, instructions that were given to all readers were as follows: "Read for highest sensitivity and negative predictive value. Read with the mindset of being afraid to miss the diagnosis of appendicitis. And search carefully for appendicitis; do not give equivocal readings."

As far as the submitted image database, of the 203 patients that were enrolled, all 203 patients had images collected by the independent contractor from the site, and formatted into an image database that was submitted to us for review. Of these 203 patient, 200 patients had digital image data, and 3 had films that were scanned in. The submitted database was organized for our viewing by site and patient number, and all 203 images were reviewed by myself.

The CDER image assessment was based on the following: the adherence to the protocol; the completeness of the dynamic and planar dataset, that is collection of 10 sequential image sets for the dynamic phase, and all 5 static image sets; and then verification or validation of time that the image became positive.

Image quality assessment further looked at the ease of image contrast and color display, which we were able to do with ease whether the patient information was redacted from the images, i.e., the name and site number being redacted, and that was performed. And then as I mentioned, the completeness of the data set.

Note that images were considered evaluable for efficacy if they had a minimum of 30 minutes worth of imaging. And this was performed in 202 out of 203 patients. As far as the completeness of the dynamic set, all patients had dynamic acquisition, however, a complete data set

consisting of 10 sequential images was found in 97 percent of patients. So what I mean by that was of the patients that were missing the complete data set, they had approximately 5-9 images collected instead of the 10.

As far as the completeness of the static data set, it was complete, that is consisting of all 5 views in 81 percent of the patients. The most commonly missing view was the standing view. That, as you recall, was the last image required in the imaging sequence. And on review of data lists and comments made by investigators on images that were missing, the standing view was likely due to patient inability to tolerate the procedure due to pain.

Six out of 203 images that were evaluated from the image database submitted to us were technically unevaluable.

This graph depicts the time to positive scan, that is the true positive reading per reader, and depicts the time point at which each reader read the image as positive. As can be seen by 30 minutes, Reader 1 read 79 percent of the images positive; Reader 2 by 30 minutes read 82 percent of images as positive; and blinded Reader 3 read 67 percent images as positive by 30 minutes. He was the most conservative of the three.

By 60 minutes you will note that all three readers actually are reading over 95 percent of the scans as positive. And then remaining few are imaged out by 90

minutes, detected by 90 minutes.

Now I'm going to introduce Dr. Lindblad.

Agenda Item: Clinical Review - Robert Lindblad

DR. LINDBLAD: For the clinical review, I'm going to briefly go over the Phase 2 trial, and then in more depth, go over the Phase 3 trial, including the trial design, the trial results, and discussing equivocal appendicitis population, performance of the Phase 3 trial, and present some pooled Phase 2 and Phase 3 data. And then management section of the Phase 3 trial, and then briefly touch on the safety data.

In the Phase 2 trial the eligibility criteria included right lower quadrant pain, in addition to signs or symptoms or laboratory findings suggestive of atypical appendicitis. These were not specifically outlined as they were in the Phase 3 trial, but they were suggestive of perhaps having a normal white count or absence of McBurney's point tenderness. Within the Phase 2 trial, PID was excluded.

The management questionnaire that was used in the Phase 2 was modified to the same questionnaire that was eventually used in the Phase 3 trial. And in that management questionnaire the surgeons were asked to decide what the disposition of the patient was, whether they would be sent home, admitted for observation, or go to surgery.

And the likelihood of appendicitis, both before the scan, and then requested to fill out that information after the scan.

In the Phase 2 trial the performance was assessed by offsite blinded readers, and onsite readers, as was done in the Phase 3 trial. And safety was evaluated by vital signs and the laboratory data.

In the Phase 2 trial two sites were recruited. As you can see, most of the patients were at Site A, which is where Dr. Kipper is. There were 49 patients at that site, and there were 7 patients recruited at a second site, Site B. Male/Female ratios was 45-55 percent. The age range was 9-77 years of age, with a median of 27. The overall incidence of appendicitis was 50 percent in this trial, compared to the Phase 3 trial, which had a 30 percent incidence of appendicitis.

This is a brief summary of the performance in the Phase 2 trial. The aggregate blinded read is represented by the offsite reads in white. The onsite reads are represented in yellow. And I present it this way so that you could actually see the numbers in terms of the true positives, which are here, false negatives. These are the false positives and the true negatives. These give you the sensitivity for the offsite read of 89 percent. The specificity of the offsite read is 68 percent. The

sensitivity for the onsite read is 96 percent, and the specificity of 79 percent.

There was a positive predictive value of 74 percent for the offsite read, and 82 percent for the onsite read, and a negative predictive value of 86 percent for the offsite read, and 95 percent for the onsite reads.

Based on these results, a Phase 3 trial was planned and implemented. And I'll go over the eligibility criteria in that, the management questionnaire, the Phase 3 trial results, and again trying to tease out of the equivocal appendicitis patient population within that trial based on the eligibility criteria, the surgeon's pre-scan disposition plan, the surgeon's pre-scan likelihood estimate. And then go over the performance for all evaluable subjects, and then also some subgroups. And then go over the management phase.

The eligibility criteria as you heard from Palatin included an atypical history, which was subdivided into four categories: no gradual onset of pain; pain that was not increasing in intensity; pain not aggravated by movement or coughing; and pain that was not migrating to the lower quadrant.

The atypical physical exam was subdivided into three categories including: the absence of McBurney's point tenderness; there was no referred tenderness with palpation

of other portions of the abdominal; and no abdominal wall spasm with right lower quadrant pain.

Additional criteria included a temperature of less 101 degree F and a white count of less than 10,500. What's important in this is only one of these nine criteria, the four from the atypical history, the three from the atypical physical exam, the temperature or the white count need to be present for the patient to qualify for this study. And as was mentioned in the Palatin presentation, women with PID were excluded, and this exclusion was based on the pelvic exam before the patient was enrolled into the study. And if the pelvic exam was suggestive of PID, the patient would then be excluded.

The management questionnaire in the Phase 3 trial was the one that was developed in the Phase 2 trial, and used to assess the clinical utility of LeuTech. Surgeons were asked to assess the anticipated disposition, and the likelihood of appendicitis both before the scan, and after the scan.

On the surgeon's management questionnaire likelihood estimates were defined into five subcategories: 0-19 percent representing a category that was verbally defined as almost definitely not appendicitis; to 80-100 percent likelihood of appendicitis, which was really defined as almost definitely having appendicitis.

In the Phase 3 trial there were 10 sites. The sites enrolled between 19 and 39 subjects per site. Four sites had less than or equal to 11 subjects. Sixty percent male and 40 percent female in the Phase 3 trial. The age range dropped from the low of 5 up to 85, with a median of 26. In this trial there was a 30 percent incidence of appendicitis compared to the 50 percent incidence in the Phase 2 trial. And the incidence per site ranged from 0-75 percent.

Next I would like to discuss the equivocal appendicitis patient population from the Phase 3 trial, our look at this based on the entry criteria, the absence of classical signs and symptoms of appendicitis, also based on the surgeon's pre-scan disposition plan, and finally on the surgeon's pre-scan likelihood estimates.

If you look at the incidence of the appendicitis that is broken down by the number of positive entry criteria, if you remember before there were a possible of nine entry criteria that would qualify for this study, if a patient one positive atypical finding, and there were 14 patients that fell into that group, the incidence of the site was 71 percent. If they had two positive entry criteria or two atypical findings, the incidence would drop down to 42 percent. This progressed all the way until 7, 8, or 9 positive atypical findings, and in those patients,

there were no cases of appendicitis.

So to look at this middle population range with 2-6 positive entry criteria, there are 172 out of the 200 evaluable patients that fell into that category, and an overall incidence of appendicitis in that group was 29 percent.

If you look at the incidence of appendicitis based on surgeon's pre-scan disposition plan, prior to getting the LeuTech scan the surgeons were asked to make a decision whether a patient should go to surgery, be admitted for observation, or sent home. There were 35 patients that the surgeons felt should go to surgery prior to getting the LeuTech scan, and based on history, physical exam, and laboratory findings. And the incidence of appendicitis was 66 percent in that group.

There were 44 patients that they felt could be sent home based on good physical exam, the history, and laboratory findings, and the incidence of appendicitis was 11 percent in that group.

And the admit for observation, the patients that the surgeons were not able to make a decision as to whether or not they needed surgery or could be sent home prior to getting the LeuTech scan, there were 121 patients in that group, and the incidence of appendicitis was 26 percent.

In the third way that I looked at the equivocal

patient population was to look at the surgeon's pre-scan likelihood estimates. Surgeons were asked prior to the scan to rank the likelihood of appendicitis. There were eight patients that fell into the 80-100 percent likelihood of having appendicitis. And in fact, the incidence of appendicitis in that group of patients was 88 percent.

This ranged down to the patients in the 0-19 percent likelihood of having appendicitis, or in other words, not very likely to have appendicitis. And in fact, none of those patients did have appendicitis.

And again, looking at this middle group of patients, those with the 20-79 percent likelihood of appendicitis based on the surgeon's pre-scan estimations, there were 170 patients that feel into that category, and the overall incidence of appendicitis in that group was 31 percent.

I'll next discuss the performance in the Phase 3 trial. This first table is similar to the Phase 2 trial performance. And then I will start looking at some subgroups, some of those based on the entry criteria, the disposition plan, the likelihood estimates, and some additional subgroups besides those.

The overall performance of the scan in the 200 evaluable patients, and as was discussed earlier, for the onsites reads the first two cases were considered training

cases. I have included those training cases in this analysis, so that both the offsite and onsite reads are based on 200 patients. And there was not a significant difference between the performance for the onsite readers, including or excluding those training cases.

For the offsite reads, the sensitivity was 75 percent, and the onsite was 90 percent; the specificity of 93 percent, and 87 percent for the onsite reads. The positive predictive value was 82 percent for the offsite read, and 74 percent for the onsite read. And the negative predictive value was 90 percent for the offsite read, and 95 percent for the onsite reads.

I have continued to use this format for most of the performance data so that you can actually look at the numbers of patients that are involved, and the number of true positives, and the number of false positives, the false negatives, and the true negatives.

This is the performance of the LeuTech scan based on six positive entry criteria. If you will remember, there were 172 patients that fell into that category. Sensitivity was 73 percent, a specificity of 93 percent, positive predictive value of 80 percent, and a negative predictive value of 90 percent.

This is based on the pre-scan disposition plan of the admitting for observation. There were 121 patients in

this group. The sensitivity was 68 percent, the specificity 93 percent, positive predictive value of 78 percent, and a negative predictive value of 89 percent.

This slide I presented a little differently, because I wanted to show all the data for the various groups. This shows the surgeon's pre-scan likelihood estimates ranging from 0-19 percent, up to 80-100 percent. This is the number of patients in each of those groups. This is the 20-79 percent, where there were 170 patients. This is the incidence of appendicitis within these entire groups.

This is the positive predictive value of the scan. In other words, if the scan was positive, the incidence of appendicitis in these groups. This column represents if the scan is negative, what is the incidence of appendicitis in these given groups going across. And then the sensitivity, specificities.

It's important to note that the positive predictive value, once you get beyond the subjects where there were no cases of appendicitis, the positive predictive value ranged from 67 percent, up to 100 percent. But there is a slow increase in the incidence of appendicitis, even with a negative scan as the likelihood of appendicitis increases. It's important to note though that this is based on eight patients. So it's difficult to make a lot of this

number, based on small number of patients.

The overall figures in the 20-79 percent range with 170 subjects, the overall incidence was 31 percent, sensitivity was 73 percent, with a specificity of 92 percent. The positive predictive value was 79 percent. In other words, it's 79 percent incidence of appendicitis in those with a positive scan. And those with a negative scan, there was an 11 percent incidence of appendicitis.

Next I would like to discuss the white blood cell count that was talked about before. If you look at the surgeon's pre-scan likelihood estimates, and you put that against the four major entry criteria, only the white blood cell count seemed to track along with the likelihood estimates. In other words, if there is a very low likelihood of appendicitis, most of those patients ended up having a normal white count.

As the incidence of appendicitis or the likelihood increased based on the surgeon's estimate, so too did the likelihood that the patients would have an elevated white count, or a decreasing likelihood that they would have a normal white count.

Looking at the data based on the white count, those patients that had a normal white count, there were 114 patients in that group, the overall incidence of appendicitis was 13 percent. Sensitivity was 60 percent in

that group, specificity was 94 percent, the positive predictive value was 60 percent, and the negative predictive value was 94 percent.

Looking at those patients that had an elevated white count, the overall incidence of appendicitis climbed significantly to 51 percent, and the number of patients was 86. Sensitivity was 80 percent, specificity was 90 percent. The positive predictive value also climbed to 90 percent, and the negative predictive value dropped somewhat to 81 percent.

I also broke out the data in terms of women between the ages of 14-35, and also within that group, those that has a 20-79 percent incidence of appendicitis based on the surgeon's pre-scan likelihood estimates. The overall incidence of appendicitis was 19 percent in that group, sensitivity was 80 percent, specificity of 95 percent, positive predictive value of 80 percent, and a negative predictive value of 95 percent. It's important to note that again, within this study PID was excluded from this patient population.

On the pediatric data, this is pooled data from Phase 2 and Phase 3. There are 15 patients between the ages of 5-9, with an overall incidence of appendicitis of 47 percent. The sensitivity was 86 percent, with a specificity of 100 percent. The positive predictive value was 100

percent, and the negative predictive value of 89 percent. Again, this is based on a very low number of patients.

The number in the 10-17 year old age group is increased to 48. The incidence is dropped to 27 percent. And again, the sensitivity is 85 percent, the specificity 92 percent, the positive predictive value of 82 percent, and a negative predictive value of 93 percent.

In the geriatric population, this is again pooled Phase 2 and Phase 3 data. There are only 12 patients in that group, and the incidence was high, 50 percent. Sensitivity was 100 percent, specificity was 83 percent, positive predictive value of 86 percent, negative predictive value of 100 percent. And again, the scan performed well, but the numbers are small.

The other group that I wanted to touch on, as you saw in the presentation from the sponsor that scans were read as positive or negative, and defined as either positive for appendicitis or positive for positive for other infection. In those that were read in for infections, and this is pooled Phase 2 and Phase 3 data, there were 30 patients from the Phase 2/Phase 3 data that had other infections; 13 of those 30, or 43 percent were false positives for appendicitis. For the onsite reads, 10 of the 30 were false positive for appendicitis, for a rate of 33 percent.

If you look at the scans that were negative, negative for appendicitis, negative for other infections, the false positive rate was 6 for the aggregate blind read out of 139 patients, or 4 percent, and it was 18 out of 139 for onsite reads, or 13 percent.

In the Phase 3 trial for the aggregate blind read, the false positive reads occurred in subjects that had other infections.

This slide has a lot of data on it, and I'll try and go through this slowly. This is trying to depict the data that the sponsor had shown in bar graphs, and I'm doing it in a table format, and hopefully they will be complementary in terms of trying to understand the shifts in management.

This is from the Phase 3 trial. This is the pre-scan disposition plan of the surgeons where they had to make a decision based on physical exam, history, and laboratory findings as to the management of the patients. They felt that 43 of these patients could be sent home, 113 would be admitted for observation, and 33 they felt would go to surgery.

These numbers are lower than the numbers that I presented earlier, and that is because we are looking at the pre-scan disposition and post-scan disposition, and 10 of these patients had their pre-scan and post-scan dispositions

filled out by different surgeons, so that they were excluded from this analysis.

For the patients that were being sent home, of those, 43 after the LeuTech scan, the decision was that 36 patients would still be sent home. And yet there were two of those patients that were positive for appendicitis. Now it's important to note that these two patients were not actually sent home. If the decision was made solely on the LeuTech scan, they would have been sent home, but the decision was made on other clinical parameters as well.

And also as was mentioned earlier, these two patients had a positive LeuTech scan, but the form was still filled out as the patient being sent home. The other was a false negative scan.

Of these 43 patients that would have been planned to have been sent home, 2 would have been admitted for observation. None of those would have had appendicitis. And 5 of the 43 that were planned to be sent home initially after the LeuTech scan would have been taken to surgery, and 3 of those actually would have had a positive appendicitis for an incidence of 60 percent.

In this group of patients, the patients where the surgeons were not clear initially whether the patient should be sent home or admitted for surgery, there were 113 patients. After the LeuTech, 39 of those 113 patients could

have been sent home based on their LeuTech scan. And if that had occurred, there would have been no patients sent home with appendicitis.

Of the 113 to admit for observation, 43 would have still been admitted for observation after the LeuTech, and 4 of those 43 ended up having appendicitis, with a 9 percent incidence. And of the 113 to admit for observation pre-scan, post-scan 31 of them would have been recommended for surgery, and the incidence of appendicitis in that group was 81 percent, 25 to 31.

In those patients finally, that the surgeons felt based on the pre-scan disposition plan to take to surgery, 26 of those still would have gone to surgery after the LeuTech scan, and 21 of those 26 would have had appendicitis for an incidence of 81 percent. Five would have been sent home. They might have gone to surgery if the LeuTech scan had not been performed, and no other testing had been done. And none of those would have had appendicitis. And two would have been admitted for observation, and again, none of those two would have had appendicitis.

So there are clearly some shifts in management based on the pre-scan data to the post-scan data. And there are some caveats that go with that. Within this shift is this pre-scan data is based on only the history, the physical exam, the laboratory findings, and is not based on

any other ancillary testing, whether it was a LeuTech scan, a CT scan, ultrasound, or any other type of imaging.

The post-scan decision was certainly made after the LeuTech scan was obtained, but it was also made after probably two hours of time, so that perhaps decisions could be made because there has been a lack of progression of symptoms, in addition to having the results of the LeuTech scan. And those are both factors that could play a role in the shifts as well.

I'll briefly touch on the safety data. It was gone over fairly completely from the sponsor. Fifty-four subjects have had HAMA evaluations, and there have been no positive HAMA reports in those patients, defined as a four-fold rise in the titre from the baseline. There were 30 normal subjects that were enrolled in this study where they were given decayed LeuTech and three weeks later given a repeat dose of LeuTech. There were five positive titres recorded in that study; two of them were mild, three moderate, and none of them were severe, and there were no clinical sequelae or adverse events related to the readministration of the decayed LeuTech.

There was one subject with the initial dose of LeuTech that had a vasodilatation effect, but that was not seen with the repeat administration.

The database for all patients that have received

LeuTech is 439 subjects. There have been no serious adverse events and no deaths. Vasodilatation has been the most event, occurring in 2.5 percent of the patients. All other adverse events have been less than 1 percent. Vital signs and laboratory parameters have been monitored both prior to and after receiving LeuTech, and again, there have been no clinically significant changes noted within these parameters.

Thank you.

DR. PONTO: At this point in time unless someone on the committee has a point of clarification for the agency, we will have a 15 minute break, and come back. And at that point in time we will have the open public meeting part of this particular meeting.

DR. LINKS: I was struck by one slide, and I'd like some clarification on it. The slide had one sentence. "A number of significant outstanding manufacturing issues remain to be resolved." I'd like a little detail on that, and I would be curious to see if the manufacturer agrees with the statement.

DR. SIEGEL: Manufacturing issues are commercial, confidential issues, if not trade secret issues, so we can't give a great deal of detail. Perhaps the manufacturer would. That was out there, however, as an important placeholder, should this committee and the agency feel

favorably about this product, often there is left with the public expectation of rapid availability of the product. It's our anticipation that will take at least a few months to resolve some of these issues, depending of course on what data show, and how quickly they can be generated.

MR. PUTNAM: I don't think we would disagree with that. We are working our way through some issues. I'm fairly confident that we can resolve them in the next couple of months.

DR. PONTO: Okay, with that we will reconvene at 10:45 a.m.

[Brief recess.]

Agenda Item: Open Public Hearing

DR. PONTO: The next item on the agenda is our open public meeting. Anyone wishing to make a comment to the issue please, identify yourself and disclose any financial renumeration for your attendance at this meeting, and please go up to the microphone. Is there anyone who would like to speak at this point in time.

Seeing no one, I have three letters that were sent to the committee. All of them are from M.D.s. The first is from William Hendricks(?). He is from Carlsbad, California.

"I would like to give you the perspective of an emergency room physician who has participated in the LeuTech

trials. The most event for the emergency physician and patient is the disposition after the evaluation has been completed. The sooner a disposition occurs, and the more accurate the diagnosis, the better it is for the patient, the emergency physician, and the limited resources of the emergency department."

"Appendicitis is the most common serious intra-abdominal disease to present in the emergency department. It is notorious difficult to diagnose, and the consequences of misdiagnoses and delayed treatment are severe. Early diagnosis and intervention results in remarkably little mortality and morbidity."

"Emergency departments across the country are overwhelmed with patients. Patients that require prolonged evaluations absorb time and resources, thereby compromising the evaluation and treatment of other patients waiting for time and space in the emergency department. The only truly dependable test for appendicitis up to this point has been observation, requiring huge allocations of emergency department time."

"Radioisotope scanning and now LeuTech has completely revolutionized the management of appendicitis at our institution. No other means of evaluation is definitive in making the diagnosis. Exam is helpful, lab is helpful, and scanning is useful, but it becomes positive way to late

in the course of the illness to make a significant difference in outcomes."

"LeuTech scanning now makes the disposition of appendicitis easy, timely, and definite. I can send a negative scan home, and admit a positive scan to surgeon. Never before I have been able to make such a definitive decision at such an early point in the natural progression of the disease. This early decision represents a tremendous benefit to the patient, yet helps me to feel comfortable with the diagnosis, it facilitates disposition so that the emergency department can be used more efficiently."

"It has been my privilege to participate in the LeuTech trials over the last few years. As you can see from the points above, appendicitis is an extremely difficult and costly diagnosis to confirm in the emergency department. LeuTech scanning has completely solved this problem."

"Sincerely, William H. Hendricks, M.D."

We have two additional e-mail messages, one from David Hoggin(?), M.D.

"As a surgeon in clinical practice in a community hospital who refers patients for LeuTech imaging as part of the Phase 3 clinical trial, I was impressed by the ease of use as compared to other approved products for labeling white blood cells, the rapid clinical results, and the effect of positive or negative LeuTech scan had on clinical

management of my patients with suspected to atypical appendicitis."

"I would request that you give full consideration to the benefits of LeuTech imaging would provide in the clinical setting for both the patients presenting with atypical appendicitis, and the physicians responsible for their care."

The third message is from Rolf Gubrinson(?), also an M.D.

"I am a general surgeon in private practice in a community hospital in Northern California, and was involved in the Phase 3 LeuTech clinical trial. The LeuTech studies were beneficial in ruling in or ruling out atypical appendicitis in several of my patients who participated in the clinical trial."

"I have had experience with other labeled white cell products, and feel that LeuTech provides significant advantages over either Technetium 99m HMPL labeled white blood cells in terms of not drawing a 30-40 cc of blood for labeling the white blood cells, the 2-4 hour time required to have the radiopharmaceutical back for reinjection of the labeled white blood cells, the potential for infection or misadministration. Both patients and physicians would benefit from the FDA approval of LeuTech in a timely manner."

These were the three messages that we received. Are there any other comments as part of the open public hearing? Please come to the microphone, and identify yourself and any potential conflicts that you may have.

DR. WAGNER: William Wagner, Immunomedics(?) Corporation, a biotechnology company.

A question dealing with the HAMA. I noticed the definition was four times baseline titre. What happens if you have somebody who has zero baseline and shows elevation following? And also if the actual time period for monitoring HAMA was appropriate? It seems to me if I read the slide correctly, it was 3-4 weeks. Is that correct? Normally, I believe you go out much further.

DR. PONTO: Would someone from the sponsor please address this question?

DR. KHAZAELI: M.B. Khazaeli, professor of medicine at the University of Alabama, Birmingham.

With over several thousand patients that we have done HAMAs on, the peak for murine monoclonal antibodies usually occurs 3-4 weeks after the injection, and after that it goes down. Our assay is different than Immunomedic's assay. It is actually a double antigen assay, which has very low non-specific binding, and four times the baseline is very reasonable criteria. Actually in our publication we have used a 3 standard deviation above the mean of the

average, plus twice as much as the background. But this one, when analyzing the data, didn't alter any of the patients' data.

DR. WAGNER: In the several cases of positives upon administration, could you say what the nanogram per mL level was in those cases?

DR. KHAZAELI: I don't know the slide number, but from memory -- okay here the most positive patients are after the second injections are listed here. It's 220 nanogram per mL, 270, and 450 nanogram per mL.

DR. WAGNER: And were those followed-up when they went down?

DR. KHAZAELI: No.

DR. WAGNER: May I ask an additional question?

DR. PONTO: Go ahead.

DR. WAGNER: On the false negatives, could you comment on that. I know you had a slide before that showed that none of them would have been sent home. I believe that was your take home message. But I guess the question is why not? Were was there overwhelming other evidence that the patients did have appendicitis?

DR. MC ELVANY: All we can say is that none were sent home. And I would assume that the surgeons made judgments based on progression of disease within that day, probably further exams or other tests. We do know that none

of them were sent home, and they all had surgery; most the same day, and one, two days later.

DR. WAGNER: In the FDA presentation that showed some of that data, and some of the subset analyses, I know I might have accumulated those patients. It was looking like the sensitivity was kind of low in some of those, which would also impact on the predictive value in that subset. I don't know if that was a particular concern. I think that was some of the material that you presented.

It struck me that the study design is sort of broad in scope, and therefore in essence you have to look at certain populations among those patients admitted to see if it was really equivocal or not. In some of the subsets that you presented, I thought were addressing that. It did seem as though the sensitivity was decreased. I don't know if that struck you as a particular problem.

DR. SIEGEL: The negative predictive value was lowest as shown in one slide, in those where the surgeon's pre-scan likelihood estimate was highest. So that would suggest in fact that where the surgeon thought the disease was probably there, a negative scan was likely to suggest the absence of disease than it was more equivocal, or thought disease was not there.

Which is in fact what we see in a lot of diagnostic areas, and one of the reasons why the study

design tried to capture both through pre-test likelihoods, as well as through pre-test planning, as well as through different manners of atypicality, and why we tried to present to the committee, data showing performance differently in those group. One typically may find different performance, particularly in predictive values based on pre-test likelihoods.

DR. PONTO: Are there any other comments as part of the open public meeting? Thank you.

DR. WHALEN: A question if I may, and tell me if I'm out of order. Although he identified himself as being with a certain company, I didn't hear if there was any interest or competing product. Just for perspective.

DR. PONTO: Would you please clarify your affiliation.

DR. WAGNER: I'm William Wagner, vice president of clinical research for Immunomedics. We are primarily a monoclonal antibody company that deals in oncology. We do have a product for infectious imaging.

DR. PONTO: Thank you very much.

Are there any other comments from the public? At this time then we will close the open public meeting portion of this meeting. And I would like to open up to the committee if there are any clarification issues that anyone on the committee would like to bring up for the sponsor or

the agency before we go into the questions.

DR. HAMMES: I have a question regarding the dose of the antibody that is being used, not the radioactivity, the antibody itself. Notably absent was any dose ranging study on the amount of antibody. And with 75-125 micrograms dosing level that was indicated is more than an order of magnitude lower than what we have seen in prior whole antibody radiolabeled approved drugs. I'm real curious if some work has been done, and if not, why not?

DR. SMITH: The antibody dose is based on the requirement of suitable antibody to achieve a 10-20 mCi labeling for dose application in infection imaging. This is a typical mCi dose range for imaging studies. Using that information, we found that 75-125 micrograms is the minimum amount of anti-CD15 that can be labeled with that quantity of radioactivity.

We did receive good efficacy with that level of the antibody. And in addition to that, we have done studies to evaluate the function of the neutrophils at levels of antibody. And we have found that if you get significantly above that, primarily 10 times above that, you do encounter some functional impact on the neutrophils. So that's the basis for selecting the microgram doses.

DR. HAMMES: Do you have any indication of what fraction of the neutrophils you are labeling with this

amount in terms of the total neutrophils? What we have seen in a lot of other of these antibodies is there is a threshold you need to achieve before you get good imaging. And you apparently haven't addressed that.

DR. SMITH: I'll ask Dr. Thakur to address that.

DR. THAKUR: The actual fraction of the neutrophils that are labeled with antibody are not known. But what do know, assuming the number of receptive(?) molecules for neutrophils, and the number of neutrophils, and taking the molecules of the antibody that we inject, each neutrophil gets about 0.4 percent of the receptors bound to the antibody molecule. So we assume uniform distribution to the cell.

Does that answer the question?

DR. ROTHSTEIN: A couple of questions about antibiotics. Is there any in vitro evidence that the antibiotics alter the binding of the antibodies? And second of all, were was there any clinical evidence in the studies the time it took for the scans to become positive was altered by patients being on antibiotics?

DR. MC ELVANY: We did look at the antibiotic dose subgroup in both safety and efficacy, which is presented in your briefing document. What we didn't look at was any effect on time to first positive, but I wouldn't expect it to be any different, because everything was pretty closely

narrowed around that in our graph. But we haven't specifically looked at time to first positive. We have no reason to believe it would be effected.

DR. BLUMENSTEIN: I'm interested in how many of the patients that have a final diagnosis of acute appendicitis were operated on, on the basis of the findings of the scan, that is would not have been operated on had the scan not been?

DR. MC ELVANY: Since this is a clinical trial of an investigational agent, none of the surgeries were based solely on the results of the LeuTech scan. It was based on the surgeon's decision, all of the clinical information, other testing, and LeuTech. So there were no patients that went to surgery based solely on a positive LeuTech scan.

DR. BLUMENSTEIN: But on the other hand, the surgeon had the LeuTech scan available in the decision to do the surgery, right?

DR. MC ELVANY: He had it available, and he could use it if he chose to, but he was instructed it was an investigational agent, and he should use it in that regard.

DR. BLUMENSTEIN: I'm also interested in whether there is any evidence that the pre-scan either probability of appendicitis scoring or the disposition, the send home, admit for observation, or surgery was in any way influenced by the knowledge that this scan would be done. In other

words, I see the danger here of a bias in the pre-scan judgment that is put down on the case report forms.

MR. PUTNAM: I can certainly see the point that you are making, but we have no way of knowing the answer to that question. The information wasn't collected. We don't know if it was influenced by the possibility that the scan would be done.

DR. BLUMENSTEIN: Here is what my problem is. I feel like sensitivity as estimated from this trial is circular. That is that there were surgeries done that wouldn't have been in the non-investigational setting. And therefore, findings of positive appendicitis, which then became part of the denominator in the estimate of sensitivity. And so that you have a kind of artificial sensitivity here.

In particular, it relates to, and this is something that I'm not an expert in at all, but it relates to what is the problem that is trying to be solved here. And in the clinical situation in normal practice, we have patients with these atypical symptoms, and many of them don't go to surgery. How many of them would have resolved had they not gone to surgery? And ultimately the bottom line question is how many unnecessary surgeries were actually done in the context of this trial?

DR. MADSEN: Kathleen Madsen, the statistician. I

think I would just like to point out that's the reason you do a blind read, I think primarily is try and get sensitivity and specificity that aren't influenced by these biases. So the results of the blind read should reflect unbiased evaluation of the efficacy.

I think the evaluation of negative laparotomy rate in and of itself is of interest, but it wasn't the direct endpoint of the trial, because we were using final diagnosis, however that was arrived at, be it following for negative patients, or surgery at some point for the eventual manifestation of appendicitis.

The slide being put up shows the 19 patients actually had false positive scans. Nine of them had no surgery, 8 had appendectomies, and 2 patients had other surgical procedures, one for a ruptured bladder, and one for a current ovarian cancer. But that's just evaluating the final outcomes of the patient.

So admittedly the investigator results always have a potential of being biased by these biases, but I think the blind read results should be free of that bias -- should be.

DR. BLUMENSTEIN: What I'm concerned about is the definition of sensitivity, and two aspects of it. Number one, that it is circular in the sense -- or at least I'm trying to get at just how circular it is in the sense that there are going to be surgeries done here that probably

would not have been done in a standard practice setting.

And then second, the sensitivity is defined in terms of a pathologic diagnosis of appendicitis, and can only be positive in the cases where there is in fact evidence of appendicitis on pathology. And so that means that a patient who doesn't have surgery, there is a presumptive diagnosis of no appendicitis based on I suppose the follow-up and whatever else. But there are no surgical results to say that there was no appendicitis.

I'm concerned that maybe there are patients who, under normal practice, would have presented with atypical symptoms, may in fact have appendicitis, not have been operated on, and are therefore not really reflected in the tables that are shown. So the actual definition of appendicitis presented isn't really a definition of appendicitis. It's a definition of a pathologic appendicitis in a sort of artificial setting. I'd like some comments on that.

DR. SIEGEL: That's a very legitimate concern, and I think it's one that can't really be addressed, certainly in the setting of this clinical trial, and I'm not sure by any design. If I understand what you are saying, you're concerned not about unnecessary surgery because of false positive, but unnecessary surgery because of true positives. People operated, the appendix was taken out, it was found to

be inflamed. Had there not been a scan, they might have gone home and done fine.

DR. BLUMENSTEIN: Exactly.

DR. SIEGEL: As they instructed, you tell the surgeon that this is an experimental test, and that's why the study collected, and we asked for post-scan disposition, which is separate from what they actually do. What the surgeons said post-scan was if you could rely on this test, if you knew this was a reliable test, what would your disposition be? They checked that down.

They checked on surgery, and they may or may not operate, but having seen the results, there is no way to know whether they did surgeries on patients who wouldn't have gone home. And there is no way to know even if those were positive, if those patients required surgery. But I think that's somewhat intrinsic. I don't think there is any way we're going to get at the answer to it.

DR. BLUMENSTEIN: That's really the heart of my concern is it's the way the data are representative. I believe that this scan is able to pick up appendicitis. The real question, is it necessary to pick up that appendicitis? And there is no data presented here to show that it is. And short of a randomized clinical trial in which you randomize between the use of the scan versus not use of the scan, maybe you have to randomize by center, rather than by

patient, but I'm concerned that the packaging and so forth like that be reflective of all of this.

And I'm concerned that the estimates of sensitivity, specificity, predictive value, positive predictive value, negative, are all conditional on this circular definition of sensitivity. And that that is really not accurate in this setting. I'm trying to figure out a way to convene that kind of information.

DR. AMENDOLA: I think that whenever this type of study is done in an investigational agent, it is one of the premises of the study that the results should not be used for a clinical decision. That is what is in every study that is done like this.

DR. BLUMENSTEIN: But in this case that's impossible.

DR. AMENDOLA: It's impossible. I agree with that.

I have another comment, and really a question. I think that there are several surgeons on the panel. I'm not a surgeon. I'm a radiologist. In this regarding one thing has been decided as a phenomenon. In other words, you get operated, and you have it or not. There are very rare instances of something that has been abortive appendicitis in which a patient gets better without surgery. That may be a cause of a problem in this kind of a study. Maybe one of

the surgeons on the panel can help us.

DR. WHALEN: Catholics are reluctant to tackle an abortion question. But I think you clearly can have episodes which are the initial pathophysiologic stages of appendicitis, and which do remit. I have seen multitudes of patients who I have operated upon who have clear cut appendicitis by anybody's definition, separated, gangarous, or perforated, as well as the histologic demonstration of same, who have had one or more antecedent episodes of where they have had vague periumbilical pain, sometimes though rarely migrating to the right lower quadrant.

Which has led to my own personal formation of the theory that it is easy to get obstruction of the lumen of your appendix, which is the initial sine qua non of the pathophysiologic step of appendicitis. And perhaps you can generate enough intraluminal pressure within your appendix to expel whatever that intraluminal obstructive focus is, and thus cut the sequence of the pathophysiology, and then at a later point have another interluminal obstruction.

I don't think you can necessarily get to the point of what would be the pathophysiologic correlate of this test, which would be true leukocytic infiltration, which would have had to have gotten to a point where intraluminal pressure exceeded venus pressure, leading to mucosal breakdown, gangrene, bacterial integration into the wall,

and then the inflammation, which leads to the right lower quadrant localization.

So that's a long winded explanation of what you are talking about, but I think you can definitely have antecedent pre-appendicitis, but generally if you are going to get to the stage which I think relates to Dr. Blumenstein's question, the test is positive, I don't think you're going to back out of that opinion.

DR. TULCHINSKY: I struggled with the same conceptual dilemma as Dr. Blumenstein has as I was reviewing the provided information. My internal conclusion was that I have to accept the study design as it was, as I could not personally conceive of a better design to answer a similar question. With life being as imperfect as it is, and the study is just reflecting that, at a certain point you have to accept the realities of it. I would be curious to hear if you had a design altering suggestion? I would be very curious to hear that, since I could not conceive of one.

Now the other side to that, which is the question I pose maybe to the investigators of the trial, is one, in their preceding practice, looking at historical data in a several prevalence of appendicitis, what was their rate of surgery performed? I think that could give some assurance that no extra or unneeded maybe or surgery just for study has occurred.

It's once again, imperfect, but it might give one an assurance that the rate of surgery performed was roughly the same as in the study population, given that the population was fairly similar. Therefore, I would very much like to hear if anything of that sort would be available for the panel to consider?

DR. CARRETTA: My name is Bob Carretta. I'm a community practitioner in Roseville, California. I was one of the Phase 3 site investigators. Mark, we have done preliminary analysis of some of that data. What we have looked at is the three month time period prior to the availability of LeuTech in the clinical trial. We looked at the negative laparotomy rate during that three month period. And it was about 20 percent, 19 point something percent. And this was all comers. This was classical appendicitis and atypical appendicitis.

When we looked at the LeuTech data and had what we would call the classical appendicitis, the negative laparotomy rate dropped to about 12 percent. And when we looked at the atypical appendicitis, the negative laparotomy rate dropped to about 7 percent. Again, this is preliminary data, and there about 35 patients in each group. We had just considered what you were saying as one way to try and go back and get some additional data. So that's the best I can do at this time.

DR. BLUMENSTEIN: Well, there is another way that that percentage can go down, and that is it's if the nature of the denominator changes. And that is if you are operating on a different type of patient than you were in the patients that were collected prior to having the scan available.

To come back to the question of a trial that would be better, there is a clear design that would be better, and that would be a randomized trial in which the randomization between the use of this scan, and not use of this scan. And the kinds of outcomes. I just happened to make a list here. Some of them would be the percent of surgeries, and since you have the randomization, just knowing the percent of surgeries would be an interesting outcome.

Percent of adverse tracks. What I mean by that is how many of the patients end up in trouble as a result of perhaps not having surgery, or perhaps having surgery and then having complications from that surgery. And I put in parenthesis cost. That's a big concern here always. And the balance would be between surgery versus observation versus the use of the scan, and so forth.

Percent accurate diagnoses as defined in this study. That would be probably the best you could do on that. And then of course the percent of surgical complications, and then the percent of other kinds of

infections found. There would be a whole host of outcomes there. These are just things I jotted down in the last couple of days.

I'm just kind of concerned that that would have been the ideal trial to do, and I understand that would be a more complicated trial. Another aspect of it that would be important to think about might be that it would be better to randomize by center, rather than by patient in order to further remove bias of the surgeon who is practicing in the setting of knowing that a scan is available on some patients. But that of course makes the trial a lot more complicated.

To answer your question, there is an ideal design I think, or a better design. As to whether that is palatable or not, I don't know.

DR. LINKS: Perhaps I'm being a tad too simplistic, but if I look at the proposed indication, it's for the diagnosis of appendicitis in patients with equivocal signs and symptoms. It is not an indication for change in management. And quite frankly, I think that all of the change in management information is icing on the cake. I think it's nice, thick, rich, delicious icing, but it is icing. Really, if you look at the indication, it seems to me it's the sensitivity and specificity that ultimately we have to judge as being appropriate or not.

I must also confess I'm a little bit confused at the practice level about some of the points you are making, because if I understand Dr. Whalen properly, if I have early appendicitis, and I operate and that's how I discover I have early appendicitis, where it might remitted if I didn't operate, the likelihood that down the road that patient is going to present again with appendicitis is rather high.

Perhaps I'm being a little glib, but you could think of the appendectomy as a prophylactic appendectomy. I think it's perhaps inappropriate to say that's surgery that is bad for the patient ultimately.

DR. BLUMENSTEIN: Let me respond to that. In 1994, I woke up on a Saturday morning with all the symptoms of appendicitis. And I was working on a very important proposal at that point in time. I called my co-investigator, and I said, oh my God, what am I going to do?

I took myself to the hospital, and I refused to allow them to operate. They kept me overnight. It resolved, and I have not had an appendectomy since. And I got the proposal done on time.

DR. LINKS: That's great, but there is no evidence you had early appendicitis.

DR. BLUMENSTEIN: It was pretty classic symptoms. It wasn't this equivocal stuff. They did not want to let me stay in the hospital overnight, because they didn't want to

spend all that time monitoring me, just as it was said here. But I just wanted to tell that personal experience. But I think your questions are really good here, and your point about the indication is a good one. Should we hold a company like this to a change in clinical management that benefits the patient, or do we take evidence that in fact this product does what it says, it finds appendicitis.

DR. SIEGEL: I should comment a little bit on the agency's approach to that distinction. We do indeed in rules recently released, that will be clarified before very long in guidance, distinguish between claims related to imaging performance, and claims related to patient management, and the types of data that are needed for them.

But in terms of data requirement, it's not quite as clear a distinction as you may make, because there is no absolute number where you say this is a good enough sensitivity or specificity or PPV or an NPV. It has to be looked at we feel, from a safety perspective if no other. The data do have to be looked at in terms of the therapeutic management implications.

If a negative test is going to cause you to miss a life saving surgery for a cancer because you say it's incurable or some such, then you may require a much different level of comfort. So yes, they are asking for a management claim, but it would wrong for the committee not