UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

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THURSDAY

MAY 15, 2003

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The meeting was held in the Grand Ballroom of the Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, Maryland, at 8:00 a.m., Dr. Polly Parsons, Chairman, presiding.

PRESENT:

POLLY E. PARSONS, M.D.	Acting Committee Chairman
KIMBERLY TOPPER, M.S.	Executive Sec.
ANDREA J. APTER, M.D., MSC	Member
T. PRESCOTT ATKINSON, M.D., Ph.D	Member
VERNON CHINCHILLI, Ph.D.	Member
ROBERT J. FINK, M.D.	Member
JESSE JOAD, M.D.	Member
PETER E. MORRIS, M.D., FACP, FCCP	Member
MICHAEL SCHATZ, M.D.	Member

CONSUMER REPRESENTATIVE:

KAREN SCHELL, RRT
ERIK R. SWENSON, M.D.

NATIONAL CANCER INSTITUTE CONSULTANT (VOTING):

GRACA DORES, M.D., M.P.H.

ACTING INDUSTRY REPRESENTATIVE (NON-VOTING)l

GEORGE OHYE

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH:

KAREN WEISS, M.D.
MARC WALTON, M.D., Ph.D.
DWAINE RIEVES, M.D.
JAMES KAISER, M.D.
PATRICK SWANN, Ph.D.

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

8:00 a.m

CHAIRMAN PARSONS: Good morning. I would like to welcome everybody to the Pulmonary and Allergy Drugs Advisory Committee Meeting. Today we are meeting to discuss BLA 103976 or Xolair which is a humanized monoclonal antibody to human IGE presented by Genentech. It's incorporated for the treatment of allergic asthma.

I would like to start with a quick reminder that if everybody can remember when they use their microphone to turn it off immediately after speaking. It would be helpful in terms of the recording of the event. We are going to start with introductions. We'll start with Dr. Ohye here at the corner. If each person could state their name and their current affiliations.

MR. OHYE: I'm George Ohye. I'm substituting for Dr. Kennedy who is the normal industry representative.

DR. DORES: I'm Graca Dores and I'm from the National Cancer Institute.

DR. SWENSON: I'm Dr. Erik Swenson from the University of Washington and I'm a Pulmonologist.

MS. SCHELL: My name is Karen Schell. I'm a Respiratory Therapist and I'm a consumer representative.

DR. SCHATZ: Michael Schatz. I'm an Allergist from Kaiser Permanente in San Diego and I'm a member of the committee.

DR. FINK: Bob Fink, Director of Pediatric Pulmonology at Children's Medical Center in Dayton, Ohio.

DR. APTER: Andrea Apter. I'm an Allergist from the University of Pennsylvania.

EXECUTIVE SECRETARY TOPPER: Kimberly Topper. I'm the Executive Secretary for the committee, FDA.

CHAIRMAN PARSONS: Polly Parsons. I'm Pulmonary and Critical Care Medicine from the University of Vermont.

DR. ATKINSON: I'm Prescott Atkinson from the University of Alabama in Birmingham in Pediatric

Allergy Immunology.

DR. CHINCHILLI: Vern Chinchilli, Biostatistics at Penn State, Hershey Medical Center.

DR. JOAD: Jesse Joad, Pediatric Pulmonologist and Allergist from the University of California at Davis.

DR. MORRIS: I'm Pete Morris. I'm at Wake Forest University in the Division of Pulmonary and Critical Care Medicine.

DR. RIEVES: I'm Dwaine rieves. I'm the Medical Officer at the Food and Drug Administration.

DR. KAISER: Jim Kaiser, Medical Reviewer at the Food and Drug Administration.

DR. WALTON: Mark Walton of Food and Drug Administration.

DR. WEISS: And Karen Weiss also at the Food and Drug Administration.

CHAIRMAN PARSONS: I'm going to ask Kimberly Topper to please present the conflict of interest statement.

EXECUTIVE SECRETARY TOPPER: The following announcement addresses the issue of conflict of

interest with regard to this meeting and is made as part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interest reported by the committee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC 208(b)(3) Dr. Michael Schatz has been granted a waiver for service on the speaker's bureaus for two competitors. He receives between $10,001 to $50,000 a year from each firm.

Dr. Robert Fink has been granted a waiver for serving on speaker's bureaus for two competitors. He receives less than $10,001 a year from one firm and from $10,001 to $50,000 a year from the other.

Dr. Andrea Apter has been granted a waiver under 21 USC 355 and 4 amendment of 505 of the Food

and Drug Modernization Act for earning stock in a competitor valued between $5,001 to $25,000. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose that Dr. George Ohye is participating in this meeting as an acting industry representative on behalf of regulated industry.

Dr. Ohye would like to disclose that he owns stock in Merck, Schering Plough, Glaxo Smith Kline, and Novartis. In December 2001 he organized a workshop that was supported by five pharmaceutical companies. Schering Plough compensated him for his work in early 2002.

Lastly, Dr. Ohye received retirement income from Novartis. In the event 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 exclusions 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 firms whose products they may wish to comment upon. Thank you.

CHAIRMAN PARSONS: I would like to start with the introduction of Dr. Patrick Swann who will be the first speaker today.

DR. SWANN: Madam Chairman, distinguished members of the Advisory Committee, ladies and gentlemen, good morning. On behalf of the Center for Biologics Evaluation and Research I would like to thank you for your participation in today's discussion concerning the use of omalizumab for the treatment of allergic asthma.

My duty today in the next few minutes is to introduce you to the BLA Review Committee and introduce the molecular entity under discussion in order to provide a brief background for the discussion of the clinical data for omalizumab.

I am Patrick Swann and I serve as the

product reviewer for omalizumab. The clinical review was the responsibility of David Essayen, James Kaiser, and Dwaine Rieves.

Pharmacology and toxicology review were performed by Hong Zhao and David Green. The statistical review was performed by Chao Wang. Research monitoring supervision was under the responsibility of J. Lloyd Johnson.

The establishment and manufacturing review for omalizumab was the responsibility of Reginald Neal. I would like to acknowledge the excellent regulatory management of Dale Slavin and Karen Jones.

The molecule for today's discussion is omalizumab, also known as Xolair, and also identified in a number of publications as E25 or ruhMAb-E25.

Omalizumab is a recombinant Chinese hamster ovary cell-derived IgG1 kappa monoclonal antibody with a molecular weight of approximately 149 kilodomes. Omalizumab binds circulating IgE regardless of IgE specificity and prevents binding

of IgE to Fc-epsilon-RI, the high affinity receptor for IgED on mast cells and basophils.

Omalizumab was designed not to bind cell-bound IgE and, therefore, should not activate mass cells and basophils and form small omalizumab IgE complexes that in vitro do not activate complement.

This concludes my brief introduction on the background. I need to remind this committee that we are still addressing some issues pertaining to the manufacture of omalizumab that remain to be resolved. The agency and Genentech are working closely together and are trying to address this issue in a timely fashion.

This concludes my presentation. I can take questions at this time or we can proceed to the next presentation.

CHAIRMAN PARSONS: Are there any questions from the group? Thank you.

We'll continue on now with Dr. Todd Rich from Genentech with an introduction and background.

DR. RICH: Good morning, Dr. Parsons, Committee Members, FDA, and guests. My name is Todd

Rich and I'm a Senior Director of Regulatory Affairs at Genentech. On behalf of Genentech and Novartis I would like to thank you for this opportunity to present our data regarding Xolair in support of the application for allergic asthma.

Specifically this morning we are pursuing an indication for Xolair as maintenance therapy for the prophylaxis of asthma exacerbations and the control of symptoms in adult and adolescents 12 years and older with moderate to severe allergic asthma that is inadequately controlled despite the use of inhaled corticosteroids.

Xolair is a subcutaneously administered humanized monoclonal antibody that is specifically designed to block IgE. It is supplied as a sterile lyophilized powder in a single use vial that will deliver 150 milligrams when reconstituted with sterile water for injection.

The original BLA for this molecule was filed in June of 2000 and included data on 17 completed clinical trials. The protocols and endpoints for these clinical trials were shared,

discussed, and thoroughly agreed to with the FDA.

At the agency's request sponsors submitted a BLA amendment in December of 2002 which included data on additional nine completed clinical trials, a newly integrated summary of safety, and a proposed indication squared on allergic asthma in adults and adolescents.

With the addition of this amendment the overall database for Xolair treated patients has increased it to include 4,200 patients. Over 3,000 patients with allergic asthma to this date have been treated with Xolair.

The data in this expanded database confirms our conclusions, that Xolair is consistently effective in clinical trials; that it decreases asthma exacerbations; that it improves asthma symptoms and pulmonary function; that it reduces steroid use; that Xolair is well tolerated with a safety profile similar to that of control; and that Xolair offers a meaningful clinical benefit to our patients.

I would like to briefly review with you

the agenda for this morning's presentation. After my opening remarks Dr. Michael Kaliner, a clinician with over 30 years of experience in treating asthma and currently the Medical Director at the Institute of Asthma and Allergy, will speak about allergic asthma and the unmet medical need that these patients present.

Dr. Charles Johnson, the Senior Director of Specialty Biotherapeutics at Genentech, will speak to you about the mechanism of action and efficacy of Xolair.

The safety portion of this morning's presentation will be handled by Dr. Andre van As, the Global Head of Respiratory Clinical Research and Development at Novartis. Finally, Dr. Kaliner will return to talk about the benefit risk of Xolair.

We also have with us this morning several experts and consultants that will be available to answer any questions the committee members may have. I've already introduced Dr. Kaliner. We also have Dr. Mark Ratain and Dr. David Spriggs as expert oncologists on drug related cancer.

Dr. Ratain is the Leon Jacobson Professor of Medicine, Chairman of the Committee on Clinical Pharmacology and Pharmacogenomics, and Associate Director for Clinical Sciences at the University of Chicago Cancer Research Center.

Dr. David Spriggs is Chief of the Developmental Chemotherapy Service and the Winthrop Rockefeller Chair of Medical Oncology at Memorial Sloan-Kettering.

Dr. Robert Tarone has been spent much of the last 30 years studying epidemiology of cancer at NCI. He is now retired from that post and is currently the Director of Biostatistics at the International Epidemiology Institute in Rockville.

Finally, Dr. Ted Warkentin, an expert on drug related thrombocytopenia, is professor of both the Department of Pathology and Molecular Medicine and the Department of Medicine at McMaster University.

With that, it is my pleasure to turn the podium over to Dr. Michael Kaliner.

DR. KALINER: Good morning. It's a

pleasure to be with friends and colleagues. I was honored when Novartis and Genentech asked me to help them present this new molecule for your consideration. I think it offers us a significant new opportunity for the treatment of asthma so I was happy to accept this opportunity.

As Todd said, I've been treating asthma for a long time and I've seen asthma therapy evolve from antiquated approaches, theophylline and tedrol some of you may remember to the current medicines we have today.

There is no question that we have the best medicines for the treatment of asthma today that we have ever had. I know that we are better able to manage asthmatics than we have ever been in the past. Why would we want to talk about this new molecule for you today? My focus this morning will be on the unmet needs that we have in the management of asthma and how this molecule should help us.

Many of you know this but let me review it quickly. Asthma is an important disease, 5 percent of the population. Costs are enormous, up to $13

billion. It turns out that the majority of these costs are attributable to a small portion of the population that continues to get sick despite medical care. 80 percent of the costs are driven by 20 percent of the population.

About 60 percent of asthmatics have an exacerbation but 16 percent have serious exacerbations leading to about 2.5 million serious exacerbations. That leads to 1.5 million ER visits, 500,000 hospitalizations, and about 16 asthma deaths per day. It is these exacerbations that tend to be the hidden cost of asthma.

About a year and a half ago these companies put together a program known as TENOR. TENOR stands for the Epidemiology and Natural History of Asthma, Outcomes and Treatment Regimens Study, better said as TENOR.

TENOR is an interesting program. I think it's going to be extremely insightful as it comes down the road. It's a three-year study. It's finished its first year. It involves 4,700 patients greater than age six. These are patients considered

to be either severe asthmatics or difficult to manage asthmatics.

The treatment is being provided by asthma specialists, largely in university centers or large institutions, and the patients are getting standard of care as suggested by the NAEPP guidelines. Every patient in TENOR is on at least one. Many of the patients are on two, three, or even more controller medications simultaneously.

Patients are being observed closely. This is not a Xolair trial and there is no patients receiving Xolair in this study. This study is really to observe the natural history of moderate to severe asthma. Something that I can't really show you much information about today because we don't have this information. Let me show you the one-year follow-up study.

This is new data. The first year was just completed. What you are looking at is brand new information. What you see here is the classification of patients as either moderate or severe asthmatics. This is their epidemiology, if

you will, in the period before the survey was completed at the end of one year of treatment.

What you can see if that in the two weeks prior to the end of the survey. In that two-week period between 7 and 12 percent of the moderate and severe asthmatics had missed work or school despite the treatment.

In the three-month period prior to the end of the survey the moderate and severe asthmatics had had unscheduled office visits in the range of 26 to 37 percent. That 24 to 44 percent of these patients had received a steroid burst in the three months prior to the survey ending.

That 6 to 14 percent had to go to the emergency room. Despite use of one to three controller medications by asthma experts, between 2 and 7 percent had been to the emergency room in the three months prior to the end of the survey.

These are disappointing data. These patients are being treated with standard of care treatment and they are still showing you exacerbations. I think that is what TENOR says.

TENOR confirms the impact of moderate and severe asthma on both patients, quality of life, and all the other things associated with exacerbations in the health care system. This is what's driving the cost.

Despite treatment by specialists employing multiple controller medications, the TENOR cohort continues to exacerbate. In my own practice we see the same thing. What we need is something to help us prevent exacerbations.

I'm fortunate to be a part of a large asthmas specialty care center. There are four asthma specialists. We see upward of a thousand new asthmatics a year and we follow thousands of asthmatics on a daily basis. We are just inundated with asthma.

Patients are referred to us by primary care doctors or by other specialists because they are difficult to manage. In our hands with the facility we have available to us most patients turn out with moderate and severe asthma to be relatively easily managed with standard of care treatment.

Despite good management some of our patients exacerbate every year and have to be treated for exacerbations.

Some patients in my population, though, no matter what I do, continue to be either constantly exacerbating or on the edge of exacerbation or, if you will, on the edge of control no matter what I do. These patients have me gravely concerned.

I have to use high-dose medications. I'm using high-dose inhaled steroids, the most potent ones available. I'm using oral steroids when I have to. I know that these products carry with them a long-term risk.

I've been treating asthma for a long time and as I've gotten down the road a bit I come to appreciate that medicines over time have cumulative effects that I am gravely concerned about and I don't want on my conscience any of the long-term sequelae that I actually know that I'm doing because I have to. I have to do what I have to do to manage the patients and they require high-dose medication.

Let me say for sure I'm concerned about

the long-term side effects of the current medicines that I have to use in this population of patients. From the patient's perspective they are really upset by exacerbations, missing school and work, having to go in for unscheduled visits or occasionally emergency room visits. And the missed activities that they have to avoid and the lifestyle disruption.

Those are really important needs that we see in the asthmatic population. As an asthma specialist I can only underline that's what we see and that's what we are managing all the time.

Asthma is a very complex disease caused by many factors. If I look at my population of patients, allergies by far are the most important single underlying cause for asthma. In the adults that I take care of, upwards of 50 percent have allergy as the underlying cause.

In the children we take care of somewhere between 70 and 90 percent, depending on the age, have allergies as the underlying cause. Allergy is the single most important underlying cause for

asthma.

Xolair reduces serum IgE. That reduces IgE mast cells, prevents activation of the allergic cascade at its very onset before it begins. That reduces airway inflammation, the underlying cause for asthma. That reduce asthma symptoms. So Xolair treated patients tend to be better and they tend to exacerbate less. It provides a novel way to treat asthma.

Let me say I am concerned today. Despite the fact that I can manage asthma better today than ever in my career, I am concerned that what I have to do will have long-term side effects. I am sure of that. I am concerned about long-term safety. I'm concerned about ongoing risk of exacerbation.

What I need in my practice is something for my severe and moderately severe patients is a novel, safe, reliable, and effective treatment that reduces asthma exacerbations in these patients. Having carefully reviewed the data before I accepted the opportunity to come and speak to you, I think Xolair provides us a very important option for these

patients.

Having summarized some of the needs, I'm going to turn the podium over to Charles Johnson who is going to talk about the mechanism of action. Thank you.

DR. JOHNSON: Thank you, Dr. Kaliner, Dr. Parsons, ladies and gentlemen. My task over the next few minutes is to outlay for you the mechanism of action of omalizumab and then to briefly review the efficacy, primarily from the pivotal studies, but I will also show you data from some of the supporting studies as well.

Omalizumab is shown here in this space-occupying model of the molecule. It is an IgG molecule and it uses a standard framework that we have used for a number of our monoclonal antibodies which is the IgG1 kappa consensus sequence.

We raise an antibody against human IgE in the mouse and we insert into this frame work the complementarity-determining or the epitome-determining region of the binding site-specific amino acids for that antibody.

There are some minor adjustments to the frame work to enhance affinity of binding to the IgE but the vast majority of this molecule, over 95 percent of it, is of human origin.

It binds circulating IgE regardless of its specificity. I will show you that in a couple of slides. It is also designed specifically that it is intended to be nonanaphylactogenic. By that we mean that if there is IgE bound to the mast cell, we have designed this molecule so that it cannot cross link IgE already bound to that mast cell.

So what happens when we insert this molecule into the allergic inflammatory cascade. This slide needs no introduction to this audience, but I would like to show you what happens when we insert IgE. Here you see large amounts of IgE being produced by plasma cells in an allergic individual.

If we bind up that IgE with Xolair, as shown in these yellow antibodies, what in fact happens is that we reduce the number of IgE molecules which are presented then on the mast cells, basophils, and eosinophils, the important

effector cells of the inflammatory system.

This, in fact, also has the effect of reducing the number of high-affinity receptors which are also available for binding to IgE. So in this situation then when you are exposed to allergens or other stimuli it tends to reduce the amount of preformed allergic mediators and, thus, subsequently reduce the secondary inflammatory response with the hope that in the end that would reduce exacerbations.

If we look specifically in some more detail, and although this is a very simplistic diagram, it illustrates two important points. Here we have the IgE molecules shown here, the anti-IgE binding to it at exactly the same site as this molecule would bind to the high-affinity receptor.

Since this is the same site, you can see that if this IgE molecule is bound here, there is no way that this molecule could, in fact, bind to the IgE once it's sitting on the mast cell. That's an important consideration for safety.

We performed a number of proof of concept

studies early in the development phase. Really the most important one is summarized here. I have taken the liberty of limiting this slide to just the active patients. This is a placebo controlled study using the broncho provocation challenge model.

A majority of patients in this small study were allergic to house dust mite and basically you challenge these patients to observe whether or not they have both the early, the short-term response drop of pulmonary function, and the late, or secondary inflammatory response, which is seen in about 30 to 40 percent of asthmatic patients.

What you see here is that after 56 days of anti-IgE therapy there is significant blunting, both of the early, and interestingly, of the late phase reaction. One thing which is not shown here is the fact that whereas in the placebo patients we were able to show an overlay at day 56 of that same early and late response so no change from baseline using the same dose of antigen challenge.

In this group of patients we actually had to increase the dose of antigen challenge two-fold

in order to generate this blunted response. It is suggested, therefore, that Xolair may play a role in allergic asthma.

To determine the dose that we would use in our Phase III studies, we used a combination of ex vivo clinical models using the basophil model generated at the Johns Hopkins Institute. We established in those early studies that cross linking degranulation of IgE on human basophils taken ex vivo is inhibited at relatively low IgE values.

It also became apparent during those experiments that this lowering of IgE was not a proportionate lowering so it wasn't a 90 or 95 percent lowering, but it had to get the IgE below a critical threshold level. That was very important for how we established our dosing.

We followed up those observations using a number of human models and looked at both asthma and rhinitis. Primarily the dose was used based on the model of rhinitis where we can look at symptoms in all of the patients during the season.

In this dose ranging study was apparent that symptom reduction in this models reached a plateau when we got free IgEs below a level of about 50 nanograms which would be equivalent to about 12 or 15 international units.

The asthma dosing then was given the biological variability both in bioavailability and response in individuals. We aim to get everybody at a mean free IgE level of about 25 nanograms per mL so that 95 percent of the population would be below that critical threshold of 50 nanograms.

Recognizing also that there is a lot of variability in the two determinants of the RPK which is IgE and body weight. We dosed patients across a relatively wide range using doses of 150 to 750 milligrams per month so that we could bring the IgE down in a wide range of patients.

The next slide shows that we were very successful in our ability to do that. It's a little complex slide but I will walk you through it. This shows on the ordinate here the median serum free IgE level in these two pivotal studies, the pediatric

study and the high-dose steroid study.

What it shows is that in each of the different dose groups, which are determined by IgE and body weight, we are able to uniformly reduce our IgE levels below that mean value of 25 nanograms per mL and show that 95 percent of the patients are below the critical value of 50 nanograms per mL.

So that is how we dose the patients. Now let us turn to the efficacy evaluation of these studies which are summarized here. The two important studies that we are going to address primarily are the two pivotal studies which are identical studies in moderate to severe allergic asthmatic patients, age 12 years and older. There were 1,071 patients there randomized equally to the two arms of the study, placebo and active.

There was a pediatric study that we will discuss briefly. A study in which we took patients who were relatively asymptomatic but had very high doses of fluticasone, more than 1,000 micrograms. We did a study in the UK and Europe which involved patients who had previously been hospitalized or in

the emergency room for their asthma.

We looked at exacerbations in those patients. We did a large safety study which was primarily to look at the safety of Xolair in patients who were on two or more controllers for their asthma. We did observe exacerbation rates in this patients as well.

The basic design of the two pivotal studies is shown in this slide and there are several important points that I would like to make. One is that the study duration during the blinded phase of the study was 52 weeks. The most important and call phase of the study was in two phases, a steroid stable phase where we kept the beclomethasone dose stable and allowed patients to use beta adrenergics, short-acting beta adrenergics as rescue medication.

We then entered an aggressive steroid reduction phase where we reduced the steroid dose by 25 percent of its baseline value every two weeks and continued to do that for a period of 12 weeks and then observed these patients at the end of that time.

In this run-in phase we changed patients from other steroids, approximately 20 percent of the sample, and adjusted the beclomethasone dose to make sure that the patients met the eligibility criteria.

The co-primary endpoints then were exacerbations both in the steroid stable and the steroid reduction phase of the trial. We defined the exacerbations as asthma worsening which required either a doubling of the baseline inhaled corticosteroid dose for at least three days, or the use of systemic corticosteroids which could use either intravenous or oral corticosteroids. As I will show you later, in the two studies about 84 percent of the patients required oral or systemic corticosteroids.

The eligibility criteria are shown here. We recruited adolescent and adult patients with IgEs in the range that we could treat; FEV1s in the moderate to severe range; beclomethasone doses of greater than 420 micrograms; a symptom score of greater than three. We used a symptom score which looked at both nighttime and daytime symptoms and

had a total value of nine.

We required that at randomization patients had a score of greater than three. We had to have positive skin tests to one of several perennial allergens. And we precluded the use of other controller medications in the pivotal trials. I will show you data from some of the supportive trials where we allowed these therapies.

The randomization was achieved successfully. Really the only difference between the two studies was that there were slightly more female patients in the 008 study than there were in the 009 study. Both groups achieved equal randomization.

In terms of the asthma characteristics of these patients, these patients have had asthma for a very long time with a mean duration of asthma of over 20 years. They were using about five to four puffs of rescue medication a day in addition to the moderate doses of beclomethasone that they were receiving.

Despite the fact that they were receiving

these doses, they had some evidence of fixed airway obstruction as evidenced by the low pulmonary function at baseline, and a small proportion of these patients had been either hospitalized or in the emergency room in the year prior to randomization.

These are the primary efficacy variables shown for the two phases of the study. We show here the stable steroid phase and then the steroid reduction phase over 12 weeks. This is the mean number of exacerbations per patient for study 008 and study 009. What you will see is very comparable reductions in the relative number of exacerbations in the two studies in the range of 40 to 60 percent. These are statistically significant.

If you turn your attention now to the right-hand side of this slide, you will see that again similar proportionate reductions in exacerbation rates in the second half of the study where we were reducing steroids aggressively in the region of 40 to 50 percent. Again, statistically significant.

One of the issues with this type of analysis is that we had imbalance in the number of dropouts during the study so we used an imputation scheme. Because there were more dropouts in the control arm it, in fact, favored the active group.

We looked at alternative methods of analysis and one of those is shown in this next slide which is a time to first event analysis, or Kaplan-Meier plot, showing the survival of patients who remain exacerbation free.

Here we have plotted not only the core phase of the study, the steroid stable and steroid production phases, but also showing you that during the extension phase we maintain that benefit. Here we see similar to those changes we showed in the first slide about a 40 to 50 percent reduction in the relative number of exacerbations and that benefit being maintained over the period of 52 weeks.

What I would draw your attention to is that if you observe these patients over that period, you will see that very nearly 50 percent of the

placebo group will, in fact, experience one of these severe exacerbations.

This is what the exacerbations looked like during the two studies. This slide basically lists for the two studies the types of exacerbation that we saw. What you will see is that there were a few patients who required either hospitalization or emergency room visit, which is significant considering that these patients were coming back for review by the investigators every two to four weeks.

Also you will note that the vast majority of patients shown here and here received systemic corticosteroids. Again, for each of these subgroups there is a trend towards a benefit in those patients receiving the active treatment.

If we look now at the amount of steroid reduction that we achieved during that second phase of the study, this is shown here as a distribution plot. It shows the proportion of patients who achieved certain amounts of reduction in their steroids.

On the left-hand side of the panel you see

complete removal of all steroids during that 12-weeks phase. And on the other extreme you see those patients who are unable to reduce or actually had to increase their steroid use.

You will see that there are almost twice as many patients who came off Xolair all together. Almost twice as many patients who had to increase or were unable to reduce their steroid dose in the placebo group. If you take that data all together, this is statistically significant.

These reductions in steroid were not at the cost of increased use rescue medication as shown here. What you see is a consistent trend across both studies towards less rescue medication in the active treated groups. During that steroid reduction phase you will see no increase in the amount of albuterol required by these patients.

If we look at the symptom scores, what I've shown here is the total symptom scores both day and night combined for the two studies. This was the primary evaluation.

On the right-hand side what I've shown to

illustrate the point that these are significant changes clinically is the nighttime wakening. If you take a patient, for example, who has a score of 1.2 on the nighttime wakening scale, this translates to a mean value of nearly 17 wakening events in a two-week period.

If you move now to this point, which is point 2, that would translate to a value of 2.8 nighttime wakening events in a two-week period. Quite a dramatic reduction in the number of wakening events for those patients during this course of the study.

Turning our attention now to the physiologic endpoint of pulmonary function, we've plotted here not only the active treatment phase but the run-in phase. What you see is typical of these types of studies where you are doing add-on therapy in a controlled clinical trial.

As you get patients ready for that randomization in the run-in phase, and we've seen this in the camp study and other studies of similar design, there is clearly an improvement in the

pulmonary function in these patients prior to randomization.

When you subsequently add to these groups the active therapy, there is an incremental improvement in pulmonary function which is maintained for the most part during that steroid reduction phase.

Putting all of that together, it's not surprising that we saw reports of improvements in quality of life. We looked at the Elizabeth Juniper asthma quality of life scale to quantify those changes. You will remember that this scale recognizes on a scale of 7 a change of .5 as being clinically detectable by patients.

So when you look at the proportion of patients who had a .5 change, you will see that a greater proportion of patients in the active group compared to the placebo group had those clinically meaningful changes.

If you look at large changes of 1.5 units, you'll see that almost twice as many of the Xolair patients achieves those changes compared to the

placebo group. Accurate documentation of using a validated model does suggest improvements in quality of life which accrue to the active group.

Briefly turning to some supporting efficacy data, this is another way of looking at exacerbations. What we do here is that we actually take the observed period for each individual patient, look at the number of exacerbations that patients has during that period, and compute the rate.

We then compare the rates for the active versus the control group. If there was no difference in those rates, then the point estimates shown as these yellow dots would lie along that line of unity. The fact that the point estimates mostly lie to the left of that curve suggest that across these studies there is a tendency for benefit in multiple different clinical situations.

This is the pediatric study where asymptomatic patients were recruited. This is the high-dose steroid study showing a trend towards reduction in exacerbations.

This is the study where we recruited patients specifically who had been in the emergency room or hospitalized the previous year. Dramatic reduction in exacerbations. This is the large safety study where there is also an actually statistically significant reduction in exacerbations in this group of patients.

If we look at the use of other controllers in some of these supporting studies, and here I have shown the UK study, but we also have similar data from the large safety study, it shows that a large proportion of these patients in these other studies were using long-acting beta-agonists, leukotriene receptor antagonists and, in fact, a small proportion of these patients were receiving oral steroids as maintenance therapy for their asthma.

If you look at those subgroups again using this analysis, you see reductions regardless of the other controller medications that these patients were using in addition to their inhales corticosteroids.

Again, to look at the consistency of the

exacerbation endpoint we present these data for your consideration which are evidence of more severe exacerbations if exacerbations required out-patient visits, emergency room visits, or even hospitalization.

We have pooled now all of those studies where we evaluated efficacy and you will see that the trend is consistent with increasing severity of exacerbations suggesting that the benefits that we saw in the pivotal studies can be translated to a number of different clinical situations.

If we now look at the studies, this is now 008 and 009 combined for the stable steroid phase, we have again done this but we are looking now at multiple different subgroups in an attempt to understand which of the populations that we studied is likely to respond to the drug.

Interestingly when you look at age, gender, race, hospitalization, or emergency room visit, baseline IgE, pulmonary function, and inhaled corticosteroid dose, you will see there is absolutely a consistent trend toward benefit

studies of the subpopulation that you look at.

This is actually a remarkable slide. When you do 17 different subgroup analyses you would expect that some of them would fall to this side of the line. The fact that none of them do attest to the consistency of this response.

So in summary, therefore, both pivotal studies have shown that Xolair reduces asthma exacerbations which require steroid interventions. These reductions are statistically significant. They are robust to alternative analyses and they are clinically relevant to patients with moderate to severe allergic asthma.

All of the other endpoints that we looked at are positive including steroid reduction symptoms and pulmonary function. The supporting studies that we've looked at show similar reductions in a wide variety of clinical situations.

I would like to turn the podium over to Dr. Andre van As who will discuss the safety of this drug.

DR. VAN AS: Dr. Parsons, members of the

Advisory Committee, and colleagues at the FDA, it is my pleasure to present the safety database to you today.

As Dr. Rich mentioned, the database has been increased significantly since our first submission to the BLA and with the resubmission we've got a larger number of patients to present safety on now.

Before going into this slide, I would just like to say from Phase I to Phase III we have treated over 6,000 patients, more than 4,000 patients having received Xolair.

This slide illustrates the populations that are going to be presented today. There will be two populations I'll be talking about mainly. These populations are drawn from the Phase IIB and III studies. The two populations are all of the patients in the Phase IIB/III studies called the all controlled studies. This consist of over 5,000 patients of which 3,000 received Xolair.

The second populations, the indicated populations -- we are also for the indication today -

- and those are the alleged asthmatic adolescents and adult patients. There were six studies there. You can see that over 3,000 patients were in this group. More than 2,000 patients received Xolair.

There were two kinds of controlled, placebo controlled and standard therapy controlled. In both instances this will be designated as control in the slides subsequently unless I specify otherwise.

The extent of exposure to Xolair was quite remarkable in this development program. You can see here that of the total of 3,200 patients more than 80 percent of patients were exposed for more than the 12 weeks. That is the usual exposure time for most asthma submissions.

Eighty-eight percent of patients were exposed for six months or longer and about a quarter of our patients were exposed for a year. So together with the size of the database and the extent of exposure, we are confident that we can describe the safety of this molecule very adequately today.

I won't go into a great deal about the design or safety because this has been mentioned in several slides, but just to mention that because of the unique way in which Xolair, which is an IgG humanized monoclonal antibody, attaches to the CH3 domain on the IgE molecule, we did not expect any excess of hypersensitivity reactions compared to the control population.

As a humanized monoclonal antibody we do not expect this protein to excite any antigenic responses. As Dr. Johnson said, it binds only to IgE and that is its mechanism of action for the efficacy and, therefore, does not reduce any other immunoglobulin levels such as IgA or IgM and IgG.

It reduces the IgE to within normal limits so we're not rendering any of these patients deficient in IgE. Preclinical data showed that there is no interference with normal immune makers, particularly cell-mediated immunity. There is also an interference with response to immunization.

The database is very large and there is a lot of information so I am going to just make a very

high-level overall statement that when we look at the frequencies of adverse events across the whole program occurring in 1 percent or more of patients, we see that there is no patent of adverse events by preferred term, no cluster of adverse events in any organs.

The majority of the adverse events, about 80 percent, were mild to moderate and were limited in duration. There is no difference in the duration of adverse events between the active treated group and the control group.

This slides shows the typical occurrence of adverse events in 5 percent or more of patients. We look here at the all-control studies and the allergic asthma control studies. If you glance at this slide, you'll see very quickly that there is really no systematic difference in the occurrence of adverse events between the active treated group and the control group.

The majority of adverse events are on the respiratory treatment, as you would expect, when studying this indication. Here, once again, you see

that there is no difference.

There is a slightly higher incidence of adverse events amongst the allergic asthma patients. This is not unexpected because these studies lasted for up to a year and there is a greater opportunity to collect adverse events in these patients.

If we turn now to serious adverse events, we see, first of all, that the total number of serious adverse events was very low resulting in a very small percentage of the patients receiving Xolair having these serious adverse events. There is not a substantial difference in the occurrence of serious adverse events between active and control treated patients.

The serious adverse events that were judged to be drug related by the investigators was identical in both groups. The occurrence of death was identical in both groups, none of the deaths being either drug related or disease related.

This gives you a flavor of the kinds of serious adverse events that occurred in four or more patients during the development program. You can

see we have shown three categories here; respiratory, gastrointestinal, and other.

Looking at the table two thing strike one. The first is that the percentage of the serious adverse events is extremely low but uniformly less than .3 percent. There is no consistent tendency for serious adverse events to occur more frequently in the Xolair treated group compared to the control groups.

As expected, or not unexpected, we saw a small number of cancers occurring in the development program. This cancer was not an exclusion criterion for patients to enter into the study. If a patient had a cancer for more than three months prior to randomization, they were allowed into the study. When we looked at the database we found that there were 20 patients with 21 cancers. This slide illustrates these cancers to you.

Four important points come out from the clinical assessment of these cancers. The first point is that if you look down the list you see that they are very heterogenous with respect to cell type

and organ origin.

I would like to run through some of these cancers to illustrate that point a little further. The skin cancer, the non-melanomas, four of these patients had tumors of a similar kind before coming into the studies.

Breast cancer, which we know is a very common phenomenon, of these five patients two patients were diagnosed four weeks after entering the study. Another two were diagnosed within 17 weeks of entry in the study. One of the patients who was diagnosed within four weeks actually palpated the lump in her breast a week before coming into the study.

The patients with prostate cancer, one of these patients had a prostatectomy two years prior to coming to the study for prostatic cancer and had a recurrence during the course of the study.

We had one patient with non-Hodgkin's lymphoma which was diagnosed 12 years before coming to the study and had a recurrence at the time of entering the study. We reviewed the histology of

the relapse and the original tumor and found that they were identical and was diagnosed as a mental cell tumor which you know is a very aggressive kind of Hodgkin tumor which always does relapse.

The patient with the adenocystic thyroid cancer had a metastatic phenomenon after entering into the study having metastases to the hilar glands. The patient with the adenocystic parotid tumor had metastases in the spine by CT scanning prior to coming into the study.

The patient with the bladder tumor had hematuria at the screening visit and then had hematuria a few weeks later and then was diagnosed as a bladder cancer.

All of these patients' case narratives were blinded to treatment. These blinded narratives were submitted to three expert oncologists who reviewed these and none of these oncologists judge these cases to be drug related. That was the second important clinical feature together with a first feature which is the heterogeneity of tumors and the fact that they are solid tumors.

The third important feature is that the majority of these cancers, 12 of the cancers out of the 20, that's 60 percent, occurred within the first six months. Being solidly indicated, these tumors must have been present prior to onset of study medication.

The fourth important point is that these patients' tumors, both in the active treatment group and the control group, occurred at about the same age. This indicates that these tumors weren't behaving in any different way as a result of being exposed to Xolair.

We had a look at occurrence of tumors numerically and looked at the point estimates. We looked at this in three different ways. The patient entry in the double-blind studies where conditions for both the active and the control treated patients who are identical. We see the point estimate gives us a rate ratio of 1.6 which is numerically not statistically significant.

Looking at all of the completed studies, the 20 patients I just described to you, we see that

the rate ratio is 1.9 and, once again, this is numerically not significantly different between the two groups.

When we removed all the non-melanoma skin cancers we see that the rate ratio increases to 3.8. But as with the other two rate ratios includes one suggesting numerically that this is not significantly different from control.

In order to compare this to an outside, we compared this to a reference data base, the NCI SEER database. The reason we did this was to assess whether there was over representation of cancer in these Xolair treated patients or under representation of cancer in the control treated patients.

The analysis which you saw in the briefing book which we submitted in our summary of safety to the agency was this analysis here of all the malignancies regardless of the fact whether they were recurrent or metastatic. This gave us observed expected rate of 1.8 with confidence intervals between 1.02 and 2.89.

In order to make this compatible with the inclusion criteria of cancer into the SEER database and the SEER database only includes primary cancers and not recurrent in metastatic cancers, we recalculated this number and find that when we match the inclusion criteria with the SEER database that the ratio is now 1.3 and the confidence intervals include 1 suggesting that this is numerically not different from the standard group. These are the data for the control group here.

To summarize this clinical summary of neoplasias we saw a small number of tumors and they were all solid tumors except one and that was a preexisting non-Hodgkin's lymphoma. These tumors were heterogenous in cell type and origin and not unexpected for this population.

There were no new cases of lymphoproliferative disease. Of importance is a very short time to tumor presentation in the majority of our patients. None of these cases were considered drug related by the panel of independent oncologists who reviewed these cases blinded to

treatment. Overall the clinical data do not suggest a causal relationship between cancer and treatment with Xolair.

If we now turn to some of the other adverse events, we looked at some important subgroups and the subgroup that we are looking at here is subgroups of age, gender, race, asthma severity by FEV1, concomitant medications, antibiotics and drug concentration in quartiles. For all of these categories we found no difference in the occurrence of adverse events.

Of importance the drug concentration by quartiles was that we looked at and compared the occurrence of adverse events in the placebo group to each quartile and there was no difference between any one of the quartiles and the placebo group.

Also of importance was that there was no increase in adverse events in patients receiving asthma medications or antibiotics compared to the control group.

Type 1 Hypersensitivity is another important subgroup that we looked at and we tested

the hypothesis that the way that Xolair interacts with IgE should not insight a Type 1 hypersensitivity reaction. We looked at the whole spectrum of Type 1 hypersensitivity reactions from urticaria to severe systemic hypersensitivity or anaphylaxis type reaction.

With regard to urticaria you can see there is no significant difference between the frequency of the occurrence of urticaria between Xolair and control patients. You can see we had quite a small number of urticaria patients in the total program.

Of importance there was also no relationship to the injection time and the occurrence of urticaria. Looking at the occurrence of concomitant urticaria and bronchospasm, we have also found that there was no substantial difference between the occurrence of this complex of symptoms between the Xolair and the control treated groups.

Turning to severe systemic hypersensitivity looking at the entire development program where patients received drugs both intravenously and subcutaneously we see here that

the incidence is identical for patients occurring in the Xolair treated group and one patient occurring in the control group.

One patient in the Xolair group, I think, deserves some mention. It's a women who had been on Xolair for several weeks who is known to be sensitive to antibiotics, sulfonamides, and penicillin. She received levofloxacin eye drops and subsequently a week later received RO levofloxacin and had typically anaphylaxis.

Fortunately she worked in an urgent care center and she was treated promptly, returned back to work in two days, went on with the treatment of Xolair and completed successfully the study with no further untoward events.

In case we missed aberrant manifestations of Type I Hypersensitivity we looked at the occurrence of skin rash throughout the development program regardless of the specificity of the skin rash. We see that in the old control studies there was a small excess of skin rashes, 6.5 versus 4.9.

When we look at the perceiver control

studies where patients have conditions of study that are identical for these other placebo group, we see that there is no difference in the occurrence of skin rash.

This difference can be explained by the fact that in the old control studies we had a number of open label studies. The patients being treated with Xolair were being seen by the physicians every two to four weeks, whereas the patients in the standard treatment group were visiting the physician's office only every three months. There is a far greater opportunity to observe adverse events in the Xolair treated patients versus control patients.

Indeed, we observed an observation bias here in favor of the control patients. This is why there is a lower incidence of adverse events in these patients.

Turning to Type III Hypersensitivity or Immune-Complex Syndrome, there were no spontaneous reported cases in the database. In case they had been missed we went into the database and looked at

symptom clusters so any association of urticaria skin rash with fever together with any other symptoms that make up this syndrome and that occurred within a two-week period. We found no symptom cluster of that kind. There was no difference between the active treatment group.

We also looked at the frequency of the individual components that could make up immune complex syndrome and found no difference in the individual components.

In addition to that, we looked for evidence of immune-complex nephropathy or any abnormalities of renal function by looking at elevation of creatinine or the development of proteinuria and there was no difference between the two treatment groups.

Every patient had Xolair antibodies measured at the end of the exposure period and there was no antibody formation detected so we are confident that Type III Hypersensitivity reactions did not occur.

Because IgE is reduced and the IgE could

potentially play a role in immune surveillance for infections, we looked at the expressions of mucosal immunity occurring at the frequency of adverse events of more than 1 percent of patients. And we looked at general adverse events and the respiratory system.

If we look at the data here we see that there is no increase in the expression of mucosal immune events in general or in the respiratory system either in the oral control studies or in the allergic asthma studies.

We looked at this in a slightly different way at the digestive system to try and identify an imbalance because of immune events. We looked here at all the patients by looking at expression of these events by all severities or the most severe expression.

We see that there is a small increase in nausea and diarrhea and vomiting in the old severities but this is not necessarily repeated consistently in the patients with the most severe expressions. We don't think that there is any

systematic increase in digestive system events.

We did the same analysis for female urogenital reproductive system and looking at the data we see that there was in the most severe events a small increase for dysmenorrhea, urinary tract infection but this is not reflected for all severities. Once again, there is no consistent increase in adverse events in the urogenital system or the reproductive system.

Turning to the lab measurements, a large number of lab measurements were done so I'm not going to go through these in great detail except to say by looking at the database very carefully we saw no clinically significant differences between treatment groups with respect to hematological variables, serum chemistry, or urinalysis.

With regard to the hematology we looked very carefully at the platelet counts in the entire database. As you are aware, during the development program we had a preclinical signal of thrombocytopenia in monkeys when they were given doses much larger than that with the patients who

were exposed to the development program.

We found no abnormalities in platelet count in the entire development program. This is summarized on this slide where we saw no evidence of drug concentration related to decrease in platelets in humans. The platelet analysis showed no treatment difference between Xolair and control.

Intensive surveillance after we observed the preclinical signal showed no evidence of acute reduction during the first two weeks of treatment or subsequently. We are confident that treatment with Xolair does not affect platelets when indicated in the dosing schedule.

Overall we can conclude then that Xolair is comparable with placebo with regard to the safety profile, particularly with regard to adverse events and serious adverse events. The clinical data do not suggest a causal relationship between Xolair and cancer.

With regard to immune responses, there was no difference between the active and control group with regard to the expression of Type I and Type III

Hypersensitivity or, indeed, the expression of infection and inflammation in the respiratory tract, the gastrointestinal tract, or the urogenital tract. There was no difference in lab measurements and platelet measurements. Xolair is safe and well tolerated.

Xolair is a novel therapy. It is the first new drug for a decade or more. It's a new class of drug for the treatment of asthma. Under these circumstances the sponsors commit to develop a prospective plan for post-approval safety surveillance.

Thank you for your attention. I will now turn the microphone back over to Dr. Kaliner to discuss the risk benefit.

DR. KALINER: Well, I'm going to try to summarize in a very few moments, because I know that time is short, the perspective I have in terms of what is the benefits to risk relationship in this trial in the patient population.

First of all, it's a new product, a novel approach to the treatment of asthma using a

humanized monoclonal antibody which I think has a safety and reliability record in reducing IgE and inhibiting allergic cascade and thereby stopping inflammation and making asthma easier to manage.

The sponsors have presented substantial data on efficacy and safety. I'm going to summarize very limited parts of this.

First of all, allergy is a common cause for asthma and IgE plays a relationship with allergy. I think that we all grew up in years past thinking that allergy might be a more mild form of asthma. I think the data has really shown that not to be the case. There is a direct relationship between allergy and asthma severity and IgE and other components of asthma severity.

Therefore, reducing IgE and reducing allergic inflammation as one of the causes of inflammation provides an important target in asthma management particularly in the moderate to severe asthmatics for whom this product is really intended.

I think there is a need for this product. In the patient population that I care for every

single day I see patients and I'm managing their asthma exacerbations. That's what I do.

That's what all of you do in your clinics, is you are managing patient's asthma exacerbations, either preventing them or giving the patients back to control levels. Current medications are excellent but they provide predictable long-term side effects which I think in the long term are significant to the patients.

These trials that Charlie reviewed for you showed decreases in endpoints that I consider to be extremely relevant to the clinical practice of asthma. I don't manage my patient's FEV1. I don't do FEV1s. I mean, I do read the FEV1s and it's one of the many parameters I employ in deciding whether a patient needs his medications adjusted.

What I look at is the patient's symptom scores, his asthma exacerbation, the likelihood of getting into trouble. That's what I management and that's what we all manage. That's the endpoint that we employ and that's the endpoint that these studies used and showed to be significantly reduced. I

think that is a terrific achievement and advance in the assessment of medications for the treatment of asthma.

In addition, all the other parameters, the asthma related ER and unscheduled medical visits, steroid use, beta-agonist use, the asthma symptoms, PFTs and quality of life were improved with this medication. I think the use of asthma exacerbations is an extraordinary step forward in the assessment of medications for the treatment of asthma.

I also like the consistency of this. This is a different slide that Charlie showed. These are patients in these four studies who exacerbated and required systemic steroids. That is the level of asthma exacerbation. When they break down the analysis by these subgroups, you can see that the patients receiving Xolair compared to placebo were significantly better.

All of them were on the left side of line of unity and that is an enormous consistency that is nice to see. I think that behooves our use of this product later on in the treatment of asthma.

Andre summarized the safety. I'm not going to review this. 4,000 patients and he looked at major adverse events. I don't see anything important there. As well as the minor adverse events. I see no evidence of immune responses to Xolair. Neoplasias, there were few events unlikely to be caused by Xolair. No bleeding issues, no drug interactions.

So as I analyze this data, Xolair appears to me to be safe, reliable, and I know it's effective in the treatment of asthma in moderate to severe patients particularly. It has an important achievement. It reduces exacerbations and, thereby, the need for urgent care allowing reduction in inhaled corticosteroid use. For me that is an extremely important endpoint because that's what I'm juggling all day long every day.

I think Xolair provides an important new option in the management of moderate to severe asthma and, as such, I think that the benefit from this product far outweighs the need.

I have been managing asthma for a long

time and I've got to tell you that the community with whom I interact, the asthma specialists, have not been as excited about a new product since the introduction of inhaled steroids 20 or 25 years ago. We honestly can't wait to have this product in our hands to use for these patients. I hope you take that into account when you are analyzing this data.

I'm going to turn the podium back to Charlie to answer questions. Thanks for your attention.

DR. JOHNSON: Thank you, Dr. Kaliner. That concludes our presentation. I would like to leave you with the last slide which is a reminder of the indication that we are requesting here which is that Xolair would be indicated for the control of symptoms and reduction of exacerbations, prophylaxis of exacerbations in adults and adolescents with moderate to severe allergic asthma which is fully controlled despite the use of inhaled corticosteroids.

CHAIRMAN PARSONS: We are going to open this up to questions from the committee. I think I

would like to start with one actually. Can we get a look at that last slide again? Can you just clarify the indication? Is this for asthma or allergic asthma?

DR. JOHNSON: It's for allergic asthma.

CHAIRMAN PARSONS: Okay. I think that is an important distinction perhaps if we go through the discussion.

DR. JOHNSON: Yes. On the bottom there it's allergic asthma.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: I have actually several questions for you about your pivotal studies. I saw no mention of smoking in the inclusion/exclusion criteria or any analysis of the effect of smoking.

DR. JOHNSON: Patients who were previous smokers were excluded from the study.

DR. FINK: Typically clinically smoking is a major cause of severe asthma. Would you then put that in your package indication that this drug is not indicated for smokers?

DR. JOHNSON: I think we would describe

the eligibility criteria for the studies and suggest that it excluded patients who were active smokers.

DR. FINK: Have you done any studies on dosage guidelines in obese patients since there is a real epidemic of obesity and it's also a risk factor for severe asthma?

DR. JOHNSON: The current dosing schedule allows us to dose patients up to 150 kilograms which is a significant -- that's about more than 300 pounds. That's a lot of body weight.

DR. FINK: If you have a relatively high IgE level and a high body weight you would be excluded under your --

DR. JOHNSON: Yes. As the agency has noted, a small proportion of patients, approximately 10 or 12 percent of patients, were excluded for a high IgE and a further small percentage, about 3 percent, were excluded for a combination of body weight and IgE.

DR. FINK: With the BDP did you do any measure of compliance of medication administration?

DR. JOHNSON: All patients filled out

diary cards over the two-week intervals between visits and were required to record their daily use of medications.

DR. FINK: Was it a standard preparation of BDP?

DR. JOHNSON: Yes, it was.

DR. FINK: Which?

DR. JOHNSON: Off the top of my head that's a good question.

DR. FINK: You are using -- with the doses that were average it was a fairly large number of puffs per day?

DR. JOHNSON: Yes. The mean doses were in the region of 500 to 600 micrograms a day.

DR. FINK: Which would be five to 10 puffs a day?

DR. JOHNSON: Yes.

DR. FINK: Could you comment on why you chose BDP rather than one of the generally considered to be more active inhaled corticosteroids?

DR. JOHNSON: Yes. That really attest to

the length of time that we have been studying this drug. We used beclomethasone which was to an extent the standard of care in the mid-'90s. We felt that changing things during the program would add some risk to the program so we kept as many things that we could constant during the program.

DR. FINK: One final question. What recommendations do you have or concerns do you have if someone who is on Xolair were going to be traveling to an area where parasitic exposure is likely?

DR. JOHNSON: That's an excellent question. In fact, we looked very carefully at the pivotal studies which were mostly done in the U.S. and Europe. Very few patients had any evidence of parasitic infestation so we are currently doing a study in Brazil looking at both index patients and also family members with asthma and intestinal helminthic exposure. That study is ongoing.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: I have two questions for two different presenters. I guess first for Dr.

Kaliner. What is the evidence that allergic asthma is more severe or as severe as nonallergic asthma? Did you find that in the TENOR study? What was the subject selection? What patients were allergic? How are they defined?

DR. KALINER: I don't have the data on the TENOR study. I know that one of the subanalyses will be relationship of IgE to asthma severity but I haven't seen that analysis so I can't give you that information.

The data for IgE and allergy and relationship to asthma severity actually starts back with Ben Burrows' data back in Tuscan where they looked at the relationship of IgE to asthma severity and they found a direct relationship between low and too-high IgEs in asthma severity.

That is about 20-year-old data. Then Martinez and others have followed up on that and pretty well shown that asthma severity is related in part to IgE.

DR. APTER: But comparison of non-allergic with allergic asthmatics that allergic asthmatics

are as severely affected?

DR. KALINER: Yes. I mean, I think that you will find -- I'm not sure how to answer the question in one-on-one or not but the issue would be that many of the patients who have severe asthma have allergic asthma. I can't go really beyond that in. Could I say that allergic asthma is as severe as aspirin-related asthma? Probably not but I can't go beyond that.

DR. APTER: It's important because the struggle before allergic asthma.

DR. JOHNSON: If I could follow up on that question. If we look at the TENOR population that we recruited, out of those 4,700 odd patients if we look at their eligibility criteria based on body weight and IgE measurement, approximately 76 percent of those patients would be eligible for therapy.

We actually also did -- this was work that Larry Borrisch did working with us on the TENOR data set looking at relationship between IgE level and physician assessed asthma severity.

What you see is that particularly in the

pediatric patients, which is not the indication we are asking for today so these are patients less than 12 years of age, there is clearly a relationship between severity shown. The most severe patients are in red here.

As you move into the adults it's very difficult to see that relationship. In fact, it suggest that there is no relationship between severity and IgE level.

DR. APTER: My second question is for you, Dr. Johnson. In your definition of exacerbations some of it has to do with urgent visits but some of it has to do with peak flow changes. Those are by self-report or did you use --

DR. JOHNSON: No, those were documented also in the diary cards and was viewed by the physicians.

DR. APTER: So diary cards are self-report. Are they not?

DR. JOHNSON: Oh, yes they are self-report. Yes. In the patients who actually came for those unexpected visits we documented those measures

of pulmonary function as well.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: Following up on the allergic asthma, a couple of questions. One important one is how was allergic asthma defined? I think we all -- each of us may have a way of knowing. I think it is clear how it was defined for the trials. It's less clear what the indications specifically are or the package insert would say.

DR. JOHNSON: Right. And so are assessment is that allergic asthma is asthma in patients who have either history or clinical signs consistent with allergy. I think one of the most important points is that although we use skin testing to specific aeroallergens in the pivotal studies, the exacerbations that we prevented were not specifically exacerbations that were triggered by aeroallergen exposure.

We actually looked in the pivotal studies at the types of exacerbations that we were preventing. If we show this slide, what you can see is that although there were a few patients who had

allergen exposure as their documented trigger, the vast majority of patients had basically viral infections or chest infections which seemed to trigger those exacerbations.

That is sort of coming slightly off your question. The answer that we would give you is that in the studies we looked at patients had evidence of ATP but that is not an absolute requirement for the diagnosis of allergy.

About 60 to 80 percent of patients had evidence of allergic rhinitis or perennial allergic rhinitis. The vast majority of them had IgEs which were in our treatable range.

DR. SCHATZ: Just a follow-up question. I won't debate some of what you said right now but a follow-up question is in the TENOR study, which is being shown as perhaps the group of patients that this would be indicated in, what proportion of those patients had positive skin tests to perennial allergens similar to the inclusion criterion of the pivotal studies?

DR. JOHNSON: I can't remember that number

off the top of my head, quite frankly, but I could certainly get that information for you. What I can show you is that in the ALTO study, that large 1,899 patient study, we didn't require skin testing as an entry criterion.

We did, however, collect information on whether or not patients had previously had skin tests. We saw proportionately similar reductions in exacerbations in those patients who had no history of a positive skin test compared with those who had a history of a positive skin test.

DR. SCHATZ: And then just a second question. In the subgroup analyses one of the ones that didn't seem to show a difference was the age greater than 65. I was actually wondering what proportion of the safety database is in patients over age 65?

DR. JOHNSON: A small proportion of the safety database. The total exposed number of patients that we had who are over the age of 65 is 142 in the program.

CHAIRMAN PARSONS: Ms. Schell, did you

have a question?

MS. SCHELL: Yes, I did. I have a question regarding that you stated that the moderate to severe asthmatics, or the ones looked at, but in the treatment of severe asthma there are other alternatives.

Were there any comparisons done between -- I guess you only studied those that were on inhaled corticosteroids at a certain level, but when other medications were added compared to the national guidelines on the treatment of severe asthma, were there studies that compared those two? Was there the same kind of improvement with the addition of the drugs or did you just look at patients with inhaled steroids and no other?

DR. JOHNSON: Yes. So basically the one study that I showed in the presentation from the European study of previously hospitalized or emergency rooms visits, 90 percent of those patients received long-acting beta-agonists and we saw reductions in exacerbations in those patients as well as reductions in exacerbations of patients

receiving leukotrienes receptor antagonists.

We also actually looked at that in the large safety study and showed in -- that's actually E38. I'll show you one that I didn't show you in the core presentation.

Yes, please show that slide.

Again, we saw that 86 percent of patients receiving long-acting beta-agonists in that study and a reduction in exacerbations, leukotrienes 53 percent, and about 11 percent of patients receiving oral steroids as their maintenance.

Again, you see a trend towards reduction in exacerbations in those patients. We do have some experience but you are absolutely right, the pivotal studies excluded those from the evaluation.

CHAIRMAN PARSONS: Dr. Chinchilli is next.

DR. CHINCHILLI: I want to ask about compliance in the pivotal studies for the active and placebo groups. How did you monitor compliance and what data do you have on that?

DR. JOHNSON: So we monitor compliance using the diary cards. There was no evidence of

difference in the use of beclomethasone during the -- in the two groups. It's compounded a little bit by the fact that we were reducing the steroids actively in that steroid reduction phase. There was clearly greater reduction in steroids in the active group.

CHAIRMAN PARSONS: Dr. Atkinson.

DR. ATKINSON: Yes. I wanted to ask was there -- I guess skin tests were part of the criteria for definition of allergic asthma but do you have any information on reduction of skin test positivity during treatment?

DR. JOHNSON: Oh, yes. In the early studies using the intravenous preparation we were able to show significant reductions in the area of the skin test. That data I think we have available, the skin test responsivity, if you would like to see that.

At this stage of the studies we hadn't determined the asthma dosing at that stage but we looked at different doses of anti-IgE and divided them up into patients with low IgEs and high IgEs.

Here you see the baseline sum of the wheel areas. After therapy you can see that these were quite dramatically reduced in these patients.

CHAIRMAN PARSONS: Dr. Morris was next with a question.

DR. MORRIS: Yes. I have a question for Dr. van As, please. Could you comment on, please, the distribution of AEs versus age, and particularly, if you could, comment on frequencies of infections or viral infections versus age as the parameter.

DR. VAN AS: Let me clarify. With regard to age are you interested in a specific age group as a continuum?

DR. MORRIS: Say as a continuous variable.

DR. VAN AS: As a continuous variable. I don't think we computed the data as a continuous variable. The data that we showed, in fact, the very first slide I showed with the adverse events in 5 percent or more patients one of the top lines was viral infection, for example, and we didn't see any difference.

If we could show this slide, please. Here we look at adverse events from 12 to 17 and we examined the adverse event profile between Xolair and control so breaking out the 12 to 17-year-old group as opposed to the rest of the population we see that really there is no difference in adverse event expression in this group as compared to the older people.

DR. MORRIS: Would you have similar information on the spectrum of age particularly at the high end?

DR. VAN AS: Yes. We can show the slide of the patients over 65. Yes, this is the slide I want to see. This is a similar slide to the 12 to 17-year-old age group. Here, once again, looking at any event, respiratory track infection, infection viral and so on, we see that generally they are very similar.

There's a slight increase in the upper respiratory track infection in patients on Xolair. Perhaps viral infection. I draw your attention to the fact that we are looking at a very small

population group.

Our experience was that early on in our submission when we looked at smaller populations, we saw imbalances. When we looked at larger populations these imbalances went away. This is one of the reasons that we want to do a post-approval commitment to continue to study these patents.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: I have two questions. The first one, I think, is for you. It was about the lowest IgE levels based on the concerns that the FDA had that we would be perhaps lowering immunity based on IgE. I think you said, or one of you said, that it never got below a level that is seen in normal people who don't have allergic disease. Is that correct?

DR. VAN AS: Yes. I think Dr. Johnson showed a slide and we should ask him to come and talk about that. The point I was making before he comes to the podium was that we reduce IgE between 92 to 96 percent of the baseline value based on the dosing table. That is the direction we go for

efficacy. Whatever your starting IgE is, you never have less than 46 percent of that original IgE titre in your blood.

DR. JOAD: So you never get below -- you never overshoot and get below the level of a normal person is my question?

DR. VAN AS: You never wipe it out. You always have some either antigenically specific or molecular IgE left in your circulation.

DR. JOAD: And that is always more than -- at least as much as a normal person would have.

DR. VAN AS: It would be in the normal range but I'll hand it over to Dr. Johnson.

DR. JOHNSON: I think the question may be what is the normal range of IgE.

DR. JOAD: The low normal.

DR. JOHNSON: Right. Certainly there are people with IgEs out there which could be as high as 100 international units which would be 250 nanograms approximately who don't have expressions of allergic disease.

DR. JOAD: Right.

DR. JOHNSON: In people who have allergic disease you can have people with ragweed sensitivity that have IgEs in the range of 10 IUs.

DR. JOAD: Right. I'm talking about the low normal range. That's just my question is that one.

DR. JOHNSON: So, yes. Actually I can show you a slide, basically the slide that I showed you in the presentation which shows you that we bring everybody down to relatively 25 nanograms per mL. If you look at the very low levels that we were able to achieve, they are in the region of about 10 nanograms per mL.

One of the interesting things about dosing this drug is that it's an asymptotic curve so actually when you increase the dose within the therapeutic range it has very little impact on further lowering of the free IgE levels.

DR. JOAD: So would the answer to my question be that you never get below the normal level that a normal person would have?

DR. JOHNSON: Never is a very strong word

to say in biology but, yes, effectively.

DR. JOAD: Okay. That's my question.

My other question is for Dr. Kaliner, I think. The way we are presently managing exacerbations of asthma are to intensify steroids at times of exacerbations which are expected to occur, for instance, as you showed in your slide, with infections with early institution based on an action plan that is easy for a patient to follow and a jump-in with some sort of intensification of their steroids so that steroids is not necessarily a bad -- intensification that is not necessarily a bad thing.

The whole point is to get in early and aggressively and prevent morbidity, missing school, missing work, going to the ER, going to the hospital. So this kind of therapy is in my mind to be contrasted with that approach.

My question about that is that this particular study to me used a very complicated action plan. What triggered them to go on to the intensification is very complex. I could sort of

review it. I don't know if you have it on your slide but you didn't mention it.

It was peak flow less than 50 percent of the best or decrease in morning peak flow more than 20 percent on more than two to three successive days, or 50 percent increase in rescue medication on two to three successive days, or two to three successive nights.

Anyway, it was a complex action plan that would be very hard for your average person with a fifth grade education to follow. To me it seemed like it went against our usual practice which is to make an action plan easy for patients to use.

DR. JOHNSON: I think that the important point here was the protocol of defined actions were really used as guidelines for the physician investigators to assess the exacerbations. We didn't tell patients that they had to do that. We asked patients to phone their physicians if they were getting worse or having asthma attacks.

Then the physician assessed what the components of that asthma attack were. In fact,

when you look at the things which precipitated us to then define the asthma exacerbation which was based on the intervention that the physician determined, you will see that a large proportion of the triggering events, if you like, all the clinical situations were actually in a class of other.

What we were doing was basically telling the patients to come if they are not doing well, phone the physician. In addition, about 30 percent of the exacerbations that we actually observed didn't meet the criteria for the protocol defined exacerbation.

We weren't trying to complicate lives for the patients. We were actually trying to give guidelines for the physicians so that we could ensure that the exacerbations that we were looking at as protocol defined exacerbations were really something meaningful.

DR. JOAD: Was this a written action plan for them, these things that are in our little handout?

DR. JOHNSON: No, it wasn't a written

action plan.

DR. JOAD: The patients did not have a written action plan? They were just told to call the doctor if they were getting worse?

DR. JOHNSON: Yes. Some patients would have had written action plans.

DR. JOAD: That's not regular therapy now to have -- I mean, that's not by the NAEPP guidelines to not have an action plan.

DR. JOHNSON: Right. You are absolutely right. These studies were done in '95, '96. Although written action plans were suggested at that stage --

DR. JOAD: But they started in '98 and the guidelines came out in '97, I thought.

DR. JOHNSON: Yes.

DR. JOAD: Okay.

CHAIRMAN PARSONS: Dr. Swenson had a question.

DR. SWENSON: I have a couple. My first is why did you exclude people with very high IgE levels? It would seem to me that this might be a

group that clearly would benefit.

DR. JOHNSON: Right. Basically because it is very difficult to lower IgE with this drug in patients who have very high IgE levels. You would require to give them much more than the 750 milligram top dose that we are actually able to give patients at the moment.

DR. SWENSON: So why are you limited in going higher on the dose? Are you concerned about the consequences of higher dosing?

DR. JOHNSON: No. We are not concerned about the consequences of higher dosing but the current formulation of the therapy is that you need 1.2 cc's for every 150 milligrams and it starts to get a very large number of injections for the individual patient when you get up to those very high values.

DR. SWENSON: Okay. With regards to the issue of possible cancer increase in the treated patients, has the company looked into the issue of exploring this in animal models, standardized models of tumor?

DR. JOHNSON: Yeah.

DR. SWENSON: And whether this may, in fact, enhance not the appearance of new cancers but to accelerate the growth of clinically unrecognized cancers.

DR. JOHNSON: In fact, we discussed that with the agency and both parties agreed that animal models are difficult to interpret and difficult to standardize. There was an agreement that further animal model experiment would not be valuable in this situation.

CHAIRMAN PARSONS: I just have a follow-up on that. I'll jump in here. Is there any preclinical data out there at all that would suggest that using this particular agent and changing IgE levels in patients could in any way be associated with the development of malignancies?

DR. JOHNSON: Not to my knowledge.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: For Dr. Johnson. As you know, one of the principles of allergy is to define allergy not simply by the presence of a positive

skin test. Your patients were included on the basis of positive skin test to perennial allergens and it is much more difficult to gauge the clinical association between a positive skin test in a perennial allergen compared to a seasonable allergen.

Do you have any data on these patients pre- and post-treatment whether they were better able to tolerate a mite exposure or a cockroach exposure or, probably much more easily, assessed a cat or dog exposure?

DR. JOHNSON: No is the answer to the question. As I showed you in the data we had on the triggers, there was a very small number of patients who recorded specific allergens as their trigger. What I can tell you which may be helpful is that we looked at asthma exacerbations by season which would address the seasonable variation in allergen challenge but that doesn't help you with --

DR. APTER: But you didn't test for that. That wasn't one of you inclusion criteria.

DR. JOHNSON: No, it wasn't. No.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: An alternate way of looking at the tumor data, if one hypothesized that anti-IgE was not increasing the cancer risk but rather lowering IgE levels was taking away a protective benefit, that would actually fit better with the data you presented that the placebo group, which was allergic, had lower than predicted cancer risk.

It would be very hard to detect in clinical trials if what you are doing is bringing a group that has a protected effect bound to the average of those nonallergic individuals. How will you address that concept?

DR. JOHNSON: I think I would like to ask Dr. Ratain to address that concept. There is no known IgE determined anti-tumor antigen that has been found out there.

Dr. Ratain.

DR. FINK: That would also mean that the likelihood that an expert in oncology would assess the increase in tumors as being drug related would be small because it's not yet an accepted or proven

theory.

DR. RATAIN: Mark Ratain, University of Chicago. I think you are asking very good questions, but I want to point out that if one wanted to look for drug-induced cancers, one would never look during the first year after initiating a drug. One would only be looking at events after the first year.

If I could have 017, please. So this is the data from an ongoing study, 011. As you see here, there are 208 patients that were exposed to the drug for more than one year, 178 patients exposed to the drug for more than two years. This represents more than 550 patient years of exposure. More than 350 patient years of exposure beginning with year two.

You note there is one neoplasm that occurred and this is described in the briefing book, the FDA briefing book on page 91, and it's a case of colon cancer. I think this is evidence, strong evidence against Xolair causing cancer.

CHAIRMAN PARSONS: Dr. Morris, you had a

question?

DR. MORRIS: The question is the pivotal studies 8 and 9, the bulk of duration of exposure there was six months?

DR. JOHNSON: Fifty-two weeks.

DR. MORRIS: Could you comment then on how you would foresee the application of this medication say over the lifetime of an individual with allergic asthma?

DR. JOHNSON: The answer is we don't have any information like that right there.

DR. MORRIS: Could you speculate for us? How do you foresee it?

DR. JOHNSON: I think that one of the interesting questions that we will be asking in the future is whether or not this intervention would have any impact on the production or expression of allergic disease. We have no information to suggest that occurs at the moment. We have done a number of things so far.

We look at free IgE levels and once you take out the drug, those IgE levels in patients that

we've looked at return to the original baseline value. We have also looked at whether or not during treatment would we be reducing IgE production during treatment. In the Phase II studies we actually loaded patients up with high doses of anti-IgE and then reduced the dose.

As we reduced the dose and as that free IgE level came above the threshold value that we established, we saw a return of symptoms. In the short term we don't see any impact on IgE production. Whether or not over the long term we would do that has yet to be determined.

CHAIRMAN PARSONS: Can I jump in with a couple questions here regarding IgE levels? I know there's data in terms of over time of life so as you age, IgE levels decrease and that has been fairly well shown. What about in a single individual over a relatively shorter period of time? Do we have information on patients with or without allergic asthma in terms of variability and IgE levels over weeks to months?

DR. JOHNSON: We have very limited data on

that. You are absolutely right that once you get into adulthood, there is very little change in IgE levels.

One of the questions which is complete speculation is if you look at the cross-sectional analyses, say if you look at people who are now six to 12 and you compare them with people who are now in their 60s, is that truly an age related decrease in IgE levels or is it a change in the expression of allergic disease that we are seeing with the increase in asthma.

We don't know the answer to that so there are very few studies which have looked at longitudinal follow-up of IgE. The only study really was that some of the work from the Tuscan group who looked over a period of eight years and clearly showed that in adults no change over time.

In kids there tends to be an increase from age five to 12. Then in adolescents there tends to be a decrease over that time. For individual variability we actually looked at the individual patients in the placebo group and measured their

IgEs over time. There was very little change in the perennial allergic asthmatic patients during that 52 week period.

CHAIRMAN PARSONS: So that would suggest then as a practitioner if I got a single IgE level on a patient and they did not meet entry criteria, that if I retested them over and over again they would continue to not meet entry criteria?

DR. JOHNSON: Yes. We actually looked at that because, in fact, of the 2,000 or so patients who were screened for the two pivotal studies, about 140 of them had repeat IgE measurements within two weeks time. For the vast majority of those patients, it didn't change which dosing strata they fell into. Those who were high tended to stay high. Those who were low tended to say low.

CHAIRMAN PARSONS: One more question in this line. There was a pretty significant under-representation in these trials of minorities.

DR. JOHNSON: Yes.

CHAIRMAN PARSONS: Is there any data to suggest that IgE levels are different? That there

is any race influence on IgE levels, No. 1, and No. 2, is there any data on whether or not allergic asthma per se is the way you've defined it is different based on race?

DR. JOHNSON: I'm not aware of any difference in the allergic component of asthma. Clearly the intercity asthma studies have shown that allergy plays a major role in people in minorities who live in the intercity.

The answer to the question is no, there is no significant difference in IgE levels across race. Of the 400 or so patients, 500 or so patients who were not caucasian in our studies, the vast majority of those were African-American. When you look at that subset there is, again, a tendency towards improvement in terms of exacerbations, although it's not obviously sample sized enough to demonstrate significance.

CHAIRMAN PARSONS: Dr. Dores, you had a question?

DR. DORES: Yes. I have a couple of questions. No. 1 is I would like to know a little

bit more about the patient with the non-Hodgkin's lymphoma because there was conflicting data as to the history in the material that we were given.

If you could just clarify the duration of remission that the patient had been in prior to receiving the drug, and whether this patient did, in fact, undergo bone marrow transplant.

DR. JOHNSON: Yes. I would actually like to ask Dr. Spriggs to tell you about that case because he studied that case in detail.

DR. SPRIGGS: David Spriggs from Sloan Kettering. I was one of the oncologists reviewing the cases of cancer that appeared during this study. This is the lymphoma case that I think Dr. Dores is asking about.

Forty-five years old, had exactly 41 weeks on study until the event was noted. The non-Hodgkin's lymphoma was originally diagnosed in 1998. You see the transplant here was, according to the information we received, was in 1989 and then did have enlarged lymph nodes in the groin area but without retroperitoneal nodes in 1999.

The characteristics of this we thought were certainly consistent since the histologies were the same of recurrent disease late after the bone marrow transplantation.

DR. DORES: So, as far as you know, when we presented with the enlarged lymph nodes was there a biopsy done?

DR. SPRIGGS: There was a biopsy in -- which time are you requesting?

DR. DORES: Yes, in 1999 before she went on study.

DR. SPRIGGS: Not to our knowledge.

DR. DORES: I have another question. Specifically you specified that you are going to have safety surveillance after post-approval of this drug. I would like to know if there has been any surveillance of patients that entered studies perhaps in 1995, 1996, earlier on, if these patients have been followed up?

DR. JOHNSON: No, we have not followed up those patients.

CHAIRMAN PARSONS: Ms. Schell, you had a

question?

MS. SCHELL: Yes. I'm not sure if it's a question or a comment or concern but I wanted to reiterate Dr. Joad on the compliance issue and the patient recognizing the severity of their asthma.

If you just basically told them to call when they got worse, a lot of the patients in my experience in moderate to severe have a hard time recognizing when they are having problems with their asthma so they really do an objective measure to see where their asthma is at.

I was just concerned that maybe some of these patients didn't call when they were severe enough to be recognized so compliance might have been an issue there. I'm not quite sure.

As an educator of asthmatic patients one of biggest things is getting them to understand the severity of their symptoms at the time they are having them. If you just had them call in saying, "I'm worse," a lot of patients may not have called.

DR. JOHNSON: Yes, you are absolutely right, ma'am. The one thing I would say which would

account for that is that there is no reason to believe in a randomized placebo controlled trial that the patients who are maybe less compliant would fall into the active or the placebo control group. We may have missed some exacerbations which should have been counted. But our assumption in the randomized placebo control design is that they would fall into both groups.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: I wanted to go back to Dr. Parsons' comment and her concern and mine of the low numbers of minorities included in the trials. You mentioned that intercity asthma children have been shown to have allergies.

They certainly have been shown to have positive tests to cockroaches. I just wanted to say that I don't think it's clear that the reason intercity children have worse asthma has been entirely proven that it is due to allergy, that there are a lot of other factors that have yet to be studied.

DR. JOHNSON: Right. In fact, you are

absolutely right. We do need to do more work on this. In fact, on Sunday afternoon we will be having a meeting with the intercity asthma group to determine what studies we can do.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: Yes. I have a question for Dr. Ratain. I agree with you that if we are concerned about cancer, certainly we need to think about longer latency periods and one-year follow-up is short.

Since you presented the data of longer follow-up, could you tell us a little bit more about the patients in these studies; if they have been receiving medications continuously or intermittently; if any of them have been receiving medications for four years, etc.

DR. JOHNSON: Yes. In fact, during that study, the extension phase, after that first year that is continuous therapy. There was a hiatus between the first portion of the study and then the introduction of the extension study which, for some people, I think, ranged for approximately nine

months and for a lot of people was three months or less.

DR. DORES: So, in total, that seems to come up to about two years maximum?

DR. JOHNSON: No. What you saw was the extent of actual exposure in these patients. In fact, the duration of observation was slightly longer than that. There was a hiatus of therapy which is not counted on that slide. Does that answer your question?

DR. DORES: So could you tell me the longest follow-up?

DR. JOHNSON: So the longest -- I'll show you the slide here. The longest follow-up then are those 71 patients who have been followed-up for more than 42 months.

DR. DORES: Okay. Could you tell me the age group of that group of patients?

DR. JOHNSON: I can't tell you exactly the age group of those 72 that have the longest follow-up but those were the patients from the 011 study. These were adults and adolescents. Their mean age

at baseline was 39 years. There would be a large number of patients who are in the adult group there.

DR. DORES: Thank you.

CHAIRMAN PARSONS: Dr. Joad, you had a question?

DR. JOAD: Yes. I wondered if you would like to comment on the FDA's concern about the study where the oral steroid group seemed to not benefit.

DR. JOHNSON: That's an interesting question. The design of that study was different from the pivotal studies. The basic tenet of the design was similar in that it was a steroid-stable and steroid-reduction phase.

What we saw there was that a relatively small group of patients, 300 patients, of whom a subgroup were on oral steroids so there were 95 patients, I think, in that oral subgroup. Those patients were in addition to their 1,000 micrograms of fluticasone, a small dose of oral prednisone.

One of the things that we noted with that group was although they were a prespecified group for analysis, there wasn't stratification of the

randomization at baseline.

In fact, the randomization in that group failed and it's apparent that that subgroup who were randomized in the oral subgroup to Xolair had almost twice as many nighttime awakenings and were probably more severe patients.

When you adjust for that, it doesn't actually reduce the number of exacerbations relative to the control group who are receiving oral steroids. However, it does move them slightly closer towards that line of unity.

That's one group of patients of 100 patients who are receiving oral steroids who didn't appear to benefit. As I showed you in the other studies, we have actually collected more patients than that who are receiving oral steroids as their maintenance therapy and in those studies although there is an open label but yet controlled studies, we are able to demonstrate reductions in exacerbations in both the IAO4 and the ALTO study.

The other thing I think which is interesting is in the Phase II studies which was a

randomized placebo controlled study. There was a small group of patients who were again receiving oral steroids, a very small group of patients.

In the steroid reduction phase of that study we were able to show statistically significant reductions in oral steroids. I think there are aspects of the design which made it difficult for us to determine that benefit in that subgroup. It is not actually consistent with our observations in the other trials that we have done.

CHAIRMAN PARSONS: We're right at the 10:00 mark so we're going to take an exactly, I've been told, 15 minutes break. We need to be back in our seats and ready to go at 10:15. Thank you.

(Whereupon, at 10:00 a.m. off the record until 10:16 a.m.)

CHAIRMAN PARSONS: We'd like to restart the meeting if everybody could take their seats, please. I would like to start with a clarification from Dr. Kaliner from Genentech in answer to Dr. Joad's question of did patients have a written asthma exacerbation plan. The actual answer was

yes. Each person did have a written plan.

We would now like to go on to the FDA presentation. I would like to introduce Dr. James Kaiser as the first speaker.

DR. KAISER: Hello. Members of the Advisory Committee and consultants, thank you for your attention. I'm Jim Kaiser, the clinical reviewer for efficacy results on this BLA from CBER's Division of Clinical Trials.

The primary purpose of my presentation is to outline the efficacy information that Genentech has developed to support a marketing application for the recombinant human IgE for asthma. The review of safety information will be given by Dr. Dwaine Rieves.

Throughout this presentation I will refer to Genentech's product as omalizumab. This is the name given by USAN, the United States Adoptive Names Council. The proposed indication has already been stated by Genentech. I will just pass over this slide.

The proposed dose for omalizumab is

approximately 0.016 milligrams per kilogram body weight per international unit IgE per mL subcutaneously every four weeks. The dosing is once every four weeks if the total mass to be given is 150 to 300 milligrams.

If the total mass to be given is 450 to 750 milligrams, the dose is divided into two weekly doses. Doses greater than 750 milligrams per four-week period are not proposed. Importantly, body weight has to be between 30 to 150 kilograms and serum IgE has to be between 30 to 700 international units per mL.

Additionally, patients within these IgE and body weight ranges but for whom the monthly dose would be more than 750 milligrams do not qualify for treatment as their total dose is too high.

Genentech proposes that there is no need for dosing adjustment related to IgE changes over time but that dosing should be adjusted for significant changes in weight over time.

This slide shows the order of topics that I will present today. The role of IgE and the

intended mechanism of action of omalizumab have already been discussed. I won't do that again here.

I'll go on to a brief asthma clinical overview. Asthma is a chronic inflammatory condition of airways as defined in guidelines published by the National Heart, Lung, and Blood Institute in 1997. Symptoms of asthma include wheezing, breathlessness, and nocturnal awakenings.

Acute exacerbations of symptoms may be mild to severe and when severe may result in hospitalization. However, specific IgE to allergens is not identifiable in all sufferers. Consequently, not all asthma can be characterized as having an allergic basis.

While there are millions with asthma in the United States, a standard definition of allergic asthma does not exist so its prevalence is hard to pinpoint.

Commonly used medications for the treatment of asthma include short-acting beta-agonists, long-acting beta-agonists, leukotriene inhibitors, 5-lipoxygenase inhibitors, cromolyn

sodium, theophylline inhaled corticosteroids, oral corticosteroids, and other agents, troleandomycin, methotrexate, cyclosporine, other immunomodulators.

While commonly used not all of these medications have approved labeling for this use. Oral corticosteroids are reserved for more refractory patients and the other agents are also reserved for treatment refractory patients.

The National Heart, Lung, and Blood Institute categorizes asthma in four grades. Patients qualify for a grade based upon meeting one criterion within the following in categories of symptoms, nighttime symptoms, FEV1 or peak expiratory flow, or peak expiratory flow variability.

FEV1 are measurements of the amount of air movement with forced exhalation which is impaired in asthma. Specific characteristics are shown for severe persistent asthma.

It is important to note that individuals within any category may have varying degrees of difficulty of management. Some patients with severe

persistent asthma, for example, may have disease refractory to inhaled corticosteroids, or may have exacerbations that require hospitalization. Others may be managed with inhaled corticosteroids or have no history of hospitalization.

This is an overview of clinical trials submitted for efficacy considerations. Q0694g was a preliminary trial using an intravenous formulation of omalizumab made by an earlier process. It provided a rationale for continuing trials. I will not be discussing the results of this trial here.

Trials 008 and 009 were the critical efficacy trials. They will be discussed at some length here. Trial 010 was a safety trial in children that captured some of the same endpoints as the critical efficacy trials. Its design was very similar to that of those trials. I will discuss the results of that trial briefly here.

Trial 011 is of interest chiefly because of its enrollment of subjects who require oral corticosteroids upon entry. ALTO and IAO4 were open-label trials designed to determine safety.

Their usefulness in the determination of efficacy is profoundly limited.

I will summarize the results from ALTO briefly. The results of IAO4 were markedly limited in their interpretability due to design issues and dropouts and I will not discuss the results here.

I will now discuss the critical efficacy trials 008 and 009. These were identical randomized double-blind placebo controlled trials that enrolled subjects 12 to 76 years old with a history of asthma and with skin test reactivity to an environmental allergen.

Body weight and IgE had to be within proposed dosing limitations. A daily symptom score had to be greater than or equal to 3 on a 9 point scale. Subjects were to be on daily treatment but limited to moderate dose inhaled corticosteroids only.

Importantly, the trial excluded subjects who required many common asthma medications. This effectively limited the subject population to those who could be managed relatively well on inhaled

corticosteroids and some rescue medication. The phases of the trials have been discussed already by Genentech and I won't repeat them now.

Guidelines were created for the recognition of asthma exacerbations. Guidelines modified from those published by the NHLBI were also created for graded treatment of asthma exacerbations depending on severity and response to prior treatment.

Early treatment or treatment from mild exacerbations were to be with short-term beta-agonists only. Inhaled corticosteroids, then oral corticosteroids, were to be used for increased severity or refractoriness of asthma exacerbations.

The primary outcome measurement was asthma exacerbations defined as worsenings of asthma requiring treatment with oral or intravenous corticosteroid or a doubling of the inhaled beclomethasone dose from baseline.

The statistical analysis was to occur both in the stable steroid and steroid reduction phases and was based on the number of exacerbations. The

slide shows the method for handling missing data during the stable steroid phase. It should have also shown the imputation method during the steroid reduction phase.

To handle missing data the protocol called for imputation during the stable steroid phase of one exacerbation for every two weeks for subjects who discontinued in the stable steroid phase. During the steroid reduction phase the imputation was the maximum observed during the phase plus one.

The analytical population was subjects who received at least one dose. Since everyone did, this was equivalent to the intent-to-treat population in these trials.

Notable secondary endpoints included numbers of puffs of albuterol for symptomatic relief, amount of corticosteroid reduction, lung function as measured by peak flow meters and spirometry, and symptom scores in Juniper's asthma quality of life questionnaire.

This slide shows characteristics of subject screened out and included in the trials. In

the two trials nine and 12 percent of potential subjects were screened out due to having serum IgE that was too high. Five percent were screened out due to serum IgE being too low and 3 and 1.5 percent had a weight/IgE combination outside dosing limits.

The importance of the IgE screening is in the uncertainties over the applicability of dosing at extremes of dosing recommendations. Variations in IgE with time might make some patients ineligible at one time and eligible at another time.

In terms of subject characteristics, the large percent of caucasians enrolled in these trials is not entirely representative of the racial makeup of the asthma population in the U.S. Subjects were predominately aged 18 to 64 years old. 94 and 99 percent had severe persistent asthma by NHLBI criteria adapted for use in the trial.

Only a small percent of the enrolled population had been hospitalized in the past year. Most of the subjects were managed with medium dose inhaled corticosteroids and by design none were thought to require additional treatment.

Protocol violation were relatively limited and judged likely to have little impact on the results of the trials. The incidents of discontinuations was greater in placebo treated subjects. Discontinuation rates in the two trials were similar.

During the stable steroid phase 9 percent of placebo subjects discontinued versus 5 percent in the omalizumab treated group. During the steroid reduction phase discontinuations occurred at 5 versus 2 percent. However, these discontinuations did not critically affect conclusions on the primary outcome of the trial.

The table on the slide shows the primary endpoint results for the stable steroid phase. Across the top row you will see that both trials are represented. Rows represent the percent of subjects with either no exacerbations or with at least one exacerbation. This representation of the results is not Genentech's perspectively defined method of analysis. However, it is used here as a concise and clear summarization of the effect.

Most subjects did not have exacerbations seen in the top row from about 69 to 87 percent. Omalizumab treatment was associated with a drop in the number of exacerbations. The percents of subjects with at least one exacerbation were less by 8 and 18 percent in this analysis.

The p-values are based on the va Elteren test on the full distribution of the numbers of exacerbations per patient, not the dichotomized results. The effect was consistent across dosing schedules.

The table on this slide shows the primary endpoint results for the steroid reduction phase. As in the stable steroid phase most subjects did not have exacerbations during this phase either. Omalizumab treatment was again associated with a drop in the number of exacerbations. The percents of subjects with at least one exacerbation were less by 11 and 14 percent.

As before, the p-values are based on the van Elteren test on the full distribution of the numbers of exacerbations. The dichotomized

presentation is a concise summary of the effect size.

The results of the trials were subjected to sensitivity analyses examining whether the missing data imputation technique was critical in the determination of the effect of omalizumab. The protocol defined method inflated the difference between the treatment arm somewhat due to its extreme penalty for discontinuation. That in retrospect is unlikely to be realistic and the greater number of discontinuations in the placebo group.

The table on this slide shows representative analyses for trial 008 expressed as proportions of subjects with at least one exacerbation. The results are shown for the stable steroid and steroid reduction phases and for the protocol defined method of analysis and alternative analysis. The alternative analysis is calculation of rates based upon observed exacerbations with no imputation of missing data.

The treatment group difference in rates

during the stable steroid phase was 8 percent using the protocol method and 7 percent using the observed method. Intertreatment group differences in the steroid reduction phase were 11 and 5 percent respectively.

This discussion is not meant to suggest that the observed method or another particular method for handling missing data is the true method. It does show that the proportionate intertreatment group differences in exacerbation rates were sensitive to the method used to calculate them and that the methods examined did not critically change the finding of the treatment effect.

Another sensitivity analysis was an examination of the intensity of corticosteroids used for the treatment of exacerbations. The most severe exacerbations would be treated with intravenous corticosteroids while the least severe ones that qualified for the protocol definition with a doubling of inhaled corticosteroids.

There was no difference between the groups in the intensity of exacerbations as indicated by

the intensity of corticosteroids. This result was mirrored in an examination of the investigator attributed intensity of exacerbations. This suggest that there is no bias in the ascertainment of exacerbations but also that when exacerbations do occur, omalizumab treatment does not alter their severity.

Subset analyses were performed by race, sex, age, and measures of disease burden. They tended to show that the treatment effect was not lost in any of the subsets. However, there were two few subjects in the noncaucasian and 65 and over age groups to reliably distinguish differences.

A remarkable finding was that the treatment effect seemed to be restricted to subjects whose baseline FEV1 was less than 80 percent. The table on this slide which shows pooled data from trials 8 and 9 shows this result.

The phases of the trials are rows which show data for subject dichotomized at an FEV1 of 80 percent. There were approximately equal numbers of omalizumab and placebo treated subjects in the total

end.

Rates were expressed as the number of exacerbations per 100 subjects during the weeks at risk in a phase. The placebo minus omalizumab rate column all the way to the right shows that there was a remarkably smaller difference in rate, 3.9 versus 17.5, for subjects with FEV1s greater than or equal to 80 percent of predicted during the stable steroid phase and an actual difference favoring placebo during the steroid reduction phase.

More exacerbations among omalizumab subjects expressed as a negative rate difference in subjects with FEV1 greater than or equal to 80 percent of predicted.

In conclusion, omalizumab treatment was associated with the reduction in the number of exacerbations in both trials in both stable steroid and steroid reduction phases. This result was robust to different imputation techniques. Subset analyses mostly showed consistent effects except that there was little effect on subjects with baseline FEV1 greater than or equal to 80 percent of

predicted.

I will now show you other secondary outcomes of the trials. Secondary endpoints included measurements of rescue medication for asthma symptoms. There was only about a one puff difference in rescue medication use at the end of the steroid reduction phase. Since usual dosing of data agonist rescue is in two puff increments, this is of uncertain significance.

The table shows numbers and percents of subjects who were able to cease using inhaled corticosteroids or who were unable to change their corticosteroid dose. In the two trials there was a 21 and 25 percent difference between placebo and omalizumab groups in the proportions of subjects able to cease using inhaled corticosteroid. Thus, only a limited number of patients were able to entirely replace the inhaled corticosteroid with omalizumab injections.

Lung function was a secondary outcome for the trails. The table shows representative results from trial 008. Results from trial 009 were of

similar magnitude. It shows that the mean percent increase in these measurements at the end of the stable steroid and steroid reduction phases.

Baseline values for the morning peak expiratory flow rate for the two treatment groups were 321 and 328 liters per minute, and for FEV1 about 2.3 liters per second. The intertreatment differences at the end of the stable steroid and steroid reduction phases were clinically inconsequential. Symptom score and health related quality of life questionnaire intertreatment differences were also of uncertain clinical meaning.

Regarding the secondary endpoints, omalizumab treatment was associated with a small drop in rescue medication use and increased ability to decrease the use of inhaled corticosteroids and no remarkable effect on lung function. These effects, as well as the effects on symptom scores, were of uncertain clinical meaning.

This slide summarizes the results during the subsequent 24-week double-blind extension phase. There was no apparent diminution of the treatment

effect on asthma exacerbations over the duration of observation. The intertreatment differences in corticosteroid dosing seen at the end of the steroid reduction phase continued and there was a continued finding of no effect on lung function.

In conclusion, the subjects included in the critical efficacy trials were able to be managed at baseline on modest amounts of inhaled corticosteroids only. The subject population did not include those with refractory asthma.

The subject population did not include many non-caucasians or subjects in the greater than or equal to 65-year-old age group. There was a robust effect on asthma exacerbations with the exception of subjects with baseline FEV1 greater than or equal to 80 percent of predicted.

There was an effect on inhaled corticosteroid reduction after a period of omalizumab treatment. There were clinically inconsequential changes in lung function. Intertreatment differences and symptom scores and health related quality of life questionnaire were of

uncertain clinical meaning.

Trial 010 was a pediatric trial designed to measure safety but it had the same general design as the critical efficacy trials. Subjects were to be 6 to 12 years old and were to have minimal asthma symptoms and medication use.

The primary efficacy endpoint was reduction in corticosteroid after the steroid reduction phase. Exploratory endpoints included asthma exacerbations and other measurements similar to those of the critical efficacy trials.

During the extension phase every subject received omalizumab making efficacy determinations for the endpoints discussed here problematic. Results for that phase will not be discussed here.

The pattern of screening failures was similar to that of the critical efficacy trials. About 15 percent of screened subjects were excluded for IgE or IgE/body weight that would have placed them outside of the dosing limits.

Seventy-six percent of the trial population was caucasian and a relatively small

percent, 21 percent, had severe persistent asthma. Forty-four percent had moderate persistent asthma by the NHLBI criteria as adapted by Genentech.

This slide shows a table depicting a selection of the primary efficacy endpoint results reduction in inhaled corticosteroids. It shows that the proportion of subjects with complete discontinuation, that's the top row, of inhaled corticosteroids was greater in the omalizumab group. The p-value on this result using the van Elteren test was 0.001.

Importantly asthma exacerbations were an exploratory endpoint. The table on this slide shows the percents of subjects in each treatment group with at least one exacerbation during the stable steroid and steroid reduction phases. Omalizumab treatment was associated with a lower percent of subjects with at least one exacerbation during both phases.

The result was robust to several imputation techniques and subgroup analyses. And as in trials 008 and 009, the predominating route of

corticosteroids used to treat exacerbations was oral.

Compared to the critical efficacy trial population these subjects had less severe asthma. Like the critical efficacy trials, trial 010 did not demonstrate intertreatment differences in lung function, symptom scores, or rescue medication use.

In conclusion, trial 010 provided support for the finding in the critical efficacy trials of a treatment associated reduction in asthma exacerbations and inhaled corticosteroid use. However, as in the critical efficacy trials, other endpoint data showed no clinically important intertreatment differences.

I will now discuss the last randomized placebo controlled trial, trial 011. This trial was designed to enroll 350 subjects with asthma of whom 250 were to be of high-dose inhaled corticosteroids and 100 on oral corticosteroids with or without inhaled corticosteroids.

Concomitant medications were severely limited as in the critical efficacy trials. Dosing

of omalizumab was the same as in trials 008 and 009. The trial included stable steroid and steroid reduction phases and the primary endpoint of the trial was the reduction in inhaled corticosteroids among users of inhaled corticosteroids only at baseline. For this trial fluticasone propionate was the inhaled corticosteroid. Secondary endpoints included asthma exacerbations.

Screening failures for disqualifying IgE occurred to a somewhat larger extent than in the critical efficacy trials. About 21 percent of screened subjects were excluded for IgE that would have placed them outside of the dosing limits which were similar to the those of the critical efficacy trials.

At baseline 99 percent of the subjects were in the high dose category for inhaled corticosteroid use by NHLBI criteria. Of the 95 subjects on oral corticosteroids the mean dose was 10 to 11 milligram per day.

Among the group with use of inhaled corticosteroids only at baseline the percent of

subjects with an overnight hospital admission in the prior year was a little greater than that in the critical efficacy trials, 7 and 13 percent. It was much higher in the group on oral corticosteroids at baseline, 23 percent.

During the stable steroid phase 6 percent of omalizumab subjects discontinued versus 3 percent of the placebo subjects. This pattern of discontinuation was in the opposite direction to that of the critical efficacy trials.

Although there were a modest number of violations of the steroid run-in adjustment procedures, these violations didn't have an effect on the determination of the extent of steroid reductions.

The table on this slide shows the primary endpoint results, reduction in inhaled corticosteroid use. The median percent reduction from baseline use in the omalizumab group was 60. The median percent reduction in the placebo group was 50. The ranges are also shown. They were quite wide.

The p-value for the difference between the treatment groups was 0.003 using the van Elteren test controlling for dose schedule. The results expressed as percents of subjects who were able to discontinue entirely from inhaled corticosteroids were consistent.

Twenty-one percent of omalizumab subjects versus 15 percent of placebo subjects were able to discontinue inhaled corticosteroids entirely. This intertreatment group difference, about 6 percent, is somewhat less than that observed in the critical efficacy trials where it was about 10 and 17 percent.

The table on this slide shows the corticosteroid reduction results for the oral corticosteroid users, a secondary outcome. It shows that the median reduction in oral corticosteroid dose was 69 percent in omalizumab subjects and 75 percent in placebo subjects.

The p-value for this difference using the van Elteren test controlling for dose schedule was 0.675, not significant. When expressed as percents

of subjects with complete cessation, there was no difference. Forty-two percent of subjects in each treatment group were able to discontinue entirely from oral corticosteroids, thus no apparent benefit was achieved by oral steroid using patients on this measure.

An important secondary outcome was asthma exacerbations. The table on this slide shows the exacerbation data was percents of subjects with at least one exacerbation. It shows the data using both the protocol defined method of imputation, top, and no imputation.

Note that the no imputation method is not quite the -- the no imputation method is called observed on this slide. Note that the no imputation method is not quite the entire population during the steroid reduction period.

This is done -- the comparison of the methods is done to illustrate the effective imputation on the endpoint results. Recall that there were more discontinuers in the omalizumab group and, thus, imputation of exacerbations is

disadvantageous to the omalizumab group.

The stable steroid phase data are in columns to the left. The steroid reduction data, phase data, are in the columns to the right. Looking at the data for the stable steroid phase, the use of observed exacerbations only made a modest change in the proportions of subjects with at least one exacerbation, 3 percent and 1 percent. No sizable treatment effect is suggested.

The intertreatment group difference is notably smaller than that in the stable steroid phases of the critical efficacy trials. During the steroid reduction phase, the intertreatment group difference remains small but approaches the size seen in portions of the critical efficacy trials. The statistical significance was lessened due in part to the smaller sample size.

The next slide shows similar analyses of exacerbations in the oral steroid group. This slide is organized similarly to the previous one for the oral corticosteroid users. The percentage of subjects with at least one exacerbation was higher

in the omalizumab group during the stable steroid phase and similar between the reduction phase.

In the group on oral corticosteroids there was no benefit observed in reduction of exacerbations. The reason for the absence of efficacy and, in fact, inverse effect during the stable steroid phase is not definable.

Earlier today Genentech presented some discussion about why the results may have worked out this way in oral corticosteroid users suggesting that their nighttime awakenings were greater and that the randomization hadn't worked.

Histories of hospitalizations, emergency room visits, doctors visits for asthma, and missed school days overall were not notably difference however. Inhaled and oral corticosteroid use was about the same between the treatment arms. I think it is fair to say that the reason for the absence of efficacy is not definable.

Other endpoints collected were similar to those of the critical efficacy trials. In the inhaled corticosteroid users the difference in puffs

of albuterol was small, about a half to one puff per day. In the oral corticosteroids users the omalizumab subjects took about one puff per day more on average at baseline.

At the end of the reduction period the mean difference in puffs favored omalizumab by about three puffs. However, the median puff difference was less than a puff suggesting that the results were driven by a small number of subjects.

There were small changes in symptom scores of unclear significance for either corticosteroid group. There were small changes in symptom scores of unclear significance for either corticosteroid group and no notable intertreatment group differences were noted in peak flow FEV1 or FVC in either corticosteroid treatment group.

In conclusion about trial 011, there was some benefit in terms of corticosteroid reduction in the group on inhaled corticosteroids at baseline but not in reductions of oral corticosteroids among oral corticosteroid users.

Asthma exacerbation reductions in inhaled

corticosteroid users were demonstrated in the steroid reduction phase but not in the stable steroid phase.

There were no reductions in asthma exacerbations among the oral corticosteroid users. Symptom scores and lung function showed minimal differences between treatment groups.

Overall, this trial does not replicate in subjects on oral corticosteroids the treatment effects previously seen in subjects with modest use of inhaled corticosteroids who were studied in the critical efficacy trials.

Subjects on high doses of inhaled steroid may have had less benefit than that seen in the prior studies with subjects on moderate doses of inhaled corticosteroids.

I will conclude my summarization of the clinical trial data by briefly discussing ALTO. ALTO was an open-label trial enrolling a large number of subjects, 1,899, whose concomitant medication use was liberalized. The primary endpoint was safety but it also collected asthma

exacerbation data.

Screening failures due to IgE were high since this trial enrolled possibly a more representative population; that is, with liberalized concomitant medication use, this is an important finding.

The majority of screened subjects were excluded due to exceeding dosing limits. Subjects whose IgE were too low or too high amounted to 42 percent of screened subjects. An additional 17 percent were excluded from the trial due to IgE body weight combinations outside dosing limits. The enrolled subjects were similar in age and race to those of the critical efficacy trials.

In this talk I will only discuss the primary efficacy results. This slide depicts the primary efficacy results for the ALTO trial expressed both as subjects with at least one exacerbation and as a rate per subject for the trial period of 24 weeks.

This is a somewhat longer period of observation than the stable steroid or the steroid

reduction periods of the trials shown earlier. Neither treatment difference was comparable to that of the critical efficacy trials. Using the van Elteren test as in the critical efficacy trials the p-value for the intertreatment difference was 0.002.

In conclusion regarding ALTO, subjects were allowed to use concomitant medications liberally. In this sense, its population may have reflected the overall asthma population better than the critical efficacy trials. Its results were consistent with the critical efficacy trials but conclusions about its results are compromised by its open label design.

To conclude about the clinical trial efficacy data, the critical efficacy trials showed reductions in asthma exacerbations in inhaled corticosteroids users over most subgroups of disease burden with the exception of FEV1 greater than or equal to 80 percent.

The exacerbation benefit was sustained over nearly a year of observation. Reductions in inhaled corticosteroid use were seen. Other effect

measures did not show clinically notable treatment effects. The pediatric trial 010 and the open-label trial ALTO were supportive.

In trial 011 inhaled corticosteroid cessation data were supportive of but less than in the critical efficacy trials. No reductions were seen in the use of oral corticosteroids. Exacerbation rates decreased in inhaled corticosteroid users but only in the steroid reduction phase. There was no exacerbation benefit in oral corticosteroid users.

Finally, it is worth mentioning that there were no data on subjects without skin test reactivity and minimal data in subjects greater than or equal to 65 years old.

This concludes my remarks. Thank you for your attention.

DR. RIEVES: Good morning. My name is Dwaine Rieves. I will present a summary of the safety findings from the application review.

My presentation this morning will cover six major subjects as shown here. First, we will

examine an overview of the subjects and studies constituting the safety database. Then a summary of four major observation areas will follow. Specifically the serious adverse events, certain adverse events of special interest, notable laboratory and antibody formation findings, and finally a summary of the findings.

Although omalizumab has been evaluated in many clinical studies, here these studies are divided into exploratory studies the major studies. The exploratory studies examine various doses, regimens of administration, as well as iterations of the product.

The major studies are those terminal phase clinical studies in which omalizumab was administered in a manner consistent with that proposed for marketing subcutaneously in multi-dose regimens.

The major study safety database consist of data from 3,507 subjects who received omalizumab. Most of these subjects, 3,224, participated in controlled studies, while 283 of the subjects had

all their exposure data obtained from participation in uncontrolled studies. As shown on the next slide, data from the exploratory and major studies may also be grouped into other categories.

This slide shows the three major analytical groupings of the clinical studies that will be cited in this presentation. The bullet at the top of the slide identifies the group of all completed studies, a group that includes both the exploratory and major clinical studies.

The second bullet highlights the group of all controlled studies, or ACS, a group that includes allergic asthma studies, as well as studies of omalizumab use in other indications.

The third bullet highlights the group of allergic asthma controlled studies, or AACS, a group that is most directly applicable to the proposed market population. This group is limited to the allergic asthma studies and also limited to subjects 12 years of age or older, the age range identified within the proposed market indication.

Because the groups of all control studies

and allergic asthma control studies provide the most informative safety data, these groups are described in detail on the next two slides.

This slide highlights the indications and certain design features of the 12 control studies constituting the group of all control studies. The first bullet notes that seven of the major studies examined omalizumab use in allergic asthma.

All these studies ranged in duration from six months or one year and tested omalizumab dosages consistent with those proposed for marketing. These seven studies provide most, approximately 75 percent, of the omalizumab exposure data within the group.

The second bullet cites the allergic rhinitis studies. Three studies of seasonal allergic rhinitis and one study of perennial allergic rhinitis. The rhinitis studies were generally of six months or less duration and studied a variety of dosages, either those directly applicable to marketing or lower.

Omalizumab exposure within the rhinitis

studies accounts for approximately 25 percent of the safety database information. Lastly, the bottom bullet notes that information from one small study of omalizumab use in rhinitis and atopic dermatitis.

This slide highlights features of the allergic asthma control studies, or AACS group. This group is made up of two double-blind studies and two open-label studies. The double-blind studies include the major studies contributing efficacy data, study 008, 009, and 011. The double-blind studies also include study 012, a small sample size bronchoscopic study.

The subjects within these four studies provide approximately 1/3 of the omalizumab exposure data within the AACS group. The bottom bullet on this slide highlights the most notable observation on the slide, the finding that most omalizumab exposure safety data within the AACS group comes from open-label studies.

These studies include the ALTO study and study IAO4. Together subjects receiving omalizumab in these two studies provide approximately 2/3 of

the omalizumab exposure data within the AACS group.

It is important to remember that because these studies were open label knowledge of the treatment assignment may have influenced certain aspects of adverse event reporting, especially any study drug causality assessments.

This slide summarizes the baseline characteristics of subjects within the safety database. The vast majority of the subjects, 85 percent, are caucasian, and there is a slight excess, 55 percent of females within the database. The vast majority of subjects in the data were aged between 18 and 64 years. These ages accounting for 76 percent of the subjects in the group of all controlled studies.

Shown at the bottom of the slide is the relatively small extent of exposure among subjects 65 years of age or older, the geriatric population. 142 geriatric subjects or 4 percent of the subjects within the group of all controlled studies were exposed to omalizumab.

This slide shows the proportions of

subjects who discontinued the studies because of adverse events. All control study findings are shown on the first row and allergic asthma control study findings are shown on the second row.

Within both groups of study slightly more subjects receiving omalizumab discontinued because of adverse events than control subjects, 1.9 versus 0.9 percent in the group of all control studies, and 2.6 versus 1.1 percent in the group of allergic asthma controlled studies.

As noted at the bottom of this slide, no single type of adverse event or cluster of similar adverse events accounted for the slight excess of discontinuations among the omalizumab group.

The next slide begins a series of slides summarizing the most notable aspects of the series adverse events.

Subject deaths are summarized here. Overall five deaths were reported, three within the omalizumab group and two within control groups. The deaths among subjects receiving omalizumab including one associated with a motor vehicle accident and

another related to ischemic heart disease. The third death within the omalizumab group was reported from an ongoing study, a death related to meningococcal sepsis.

The relationship between the omalizumab exposure and this subject sepsis is unclear. The deaths reported among control subjects were related to a cardiac arrest in one case and a motor vehicle accident in another. Nonfatal serious adverse events are summarized on the next slide.

The first column on this slide shows the omalizumab rates and the second column the control rates. The serious adverse event rates were 4.2 versus 3.8 percent within the group of all control studies and 5.6 versus 4.6 percent within the group of allergic asthma control studies.

As noted at the bottom of this slide, no single type of serious adverse event or cluster of similar events completely accounted for the small excess of omalizumab subjects with serious adverse events. However, we will focus in the next several slides upon two specific types of serious adverse

events, the malignancy and anaphylaxis findings.

This slide summarizes the basis for focusing upon malignancy outcomes. In general the focus is supported by background concerns relating to two areas as shown in the major bullets.

Certain publication citing associations between atopy or skin reactivity and malignancy rates and the plausibility that immunosuppressive measures of anti-IgE therapy might impact the development or progression of malignancy. Several publications suggest an inverse relationship between the incidence of atopy and malignancy.

These publications imply that atopy may serve some protective role in the resistance to malignancy. However, these publications have major limitations as cited here. The observations are inconclusive. The various epidemiologic studies do not generally adjust for cigarette smoking and the studies suffer from multiple other limitations.

Nevertheless, the publications are of interest in the review of a product that may impact the atopic response. The bottom bullet notes that

the biology of an anti-IgE therapy may conceivably alter the resistance to malignancy.

Several biological mechanisms are plausible, most of which culminate in some alteration of various effector cell roles. For example, one recent publication has reported that in vitro human monocytes exhibit IgE dependent cytotoxicity towards ovarian cancer cells. Consequently, the malignancy findings from the clinical studies are of special interest. The next slide summarizes these findings.

This slide lists the number of subjects with malignancies and the types of the malignancies within the group of all completed studies. Shown are the malignancies for the omalizumab group on the left and the control group on the right. Overall, malignancies were diagnosed among 20 or 0.5 percent of the omalizumab group in five or 0.2 percent of the control group.

The lower rows list the various types of malignancies. Non-melanoma skin cancers were the most common overall accounting for five malignancies

within the omalizumab group and three among the control group, the numbers reflecting a similar incidence of these types of skin cancer.

It is the malignancies exclusive of non-melanoma skin cancer that accounted for the higher overall omalizumab rate. These other malignancies among the omalizumab group included five cases of breast cancer, two cases each of prostate, melanoma, and parotid cancer, and other single subject cases.

Within the group of omalizumab malignancies one subject had two types of malignancy, one event of melanoma and another event of non-melanoma skin cancer.

This slide shows the malignancy rates expressed in terms of events per 1,000 patient years of omalizumab or control group exposure. For example, in the first cell of this table there were 20 subjects with malignancies out of 3,160 patient years of exposure or a rate of 6.3 events per 1,000 patient years.

In this table the omalizumab rate is shown in the first column, the control rate in the second

column, and the rate difference with the 95 percent confidence interval in the third column. The first row shows the event rate for subjects with any kind of malignancy and the second row shows the rate for subjects with malignancies exclusive of non-melanoma skin cancer.

Overall, the omalizumab rate was 6.3 and the control 3.3, a rate difference of three subjects per 1,000 patient years of exposure. Exclusive of non-melanoma skin cancer the comparison shows a rate of 5.1 versus 1.3, a rate difference of approximately four subjects per 1,000 patient years of exposure.

The confidence interval on the rate difference for subjects with any malignancy includes zero while the confidence interval on the rate difference for subjects with any malignancy exclusive of non-melanoma skin cancer does not include zero, findings suggesting that the most notable concerns relate to malignancies exclusive of non-melanoma skin cancer.

This slides summarizes the malignancy rate

ratio comparisons of omalizumab to control. The second column shows the rate ratio in 95 percent confidence interval for subjects with any kind of malignancy the first row, in subjects with any malignancy exclusive of non-melanoma skin cancer the bottom row.

As you can see, the rate ratio is 1.9 for subjects with any type of malignancy and 3.8 for subjects with any malignancy exclusive of non-melanoma skin cancer. The confidence intervals on both ratios are very wide and include one. Findings suggesting that the rate ratio may vary from either no increase to a considerable increase in the malignancy risk due to omalizumab administration.

The next couple of slides will summarize the malignancy findings with respect to those from an epidemiological database. This slide summarizes the surveillance, epidemiology, and end results, or SEER database, of the National Cancer Institute.

This database contains cancer statistics from approximately 14 percent of the United States population. The demographics of the subjects within

the database are generally thought to mirror those of the U.S. population, but the database does not identify a specific population of allergic asthma subjects. Consequently, the database is useful for comparison purposes but are presented here solely as exploratory analyses.

Using the SEER database as a comparator it is possible to calculate the standardized incidence ratio, the ratio of number of observed malignancies within a data set divided by the number of malignancies one would expect within the data set based upon application of the SEER findings. The sponsor submitted analyses are summarized on the next slide.

Shown here are the observed and the expected number of malignancies exclusive of non-melanoma skin cancer. The three columns show, firstly, the number of observed malignancies in the sponsor's study. Secondly, the number of expected malignancies as adjusted by age and gender. Finally, the standardized incidence ratio.

The first row shows the omalizumab

findings and the second the control findings. Overall, 16 subjects with malignancies exclusive of non-melanoma skin cancer were observed among the omalizumab group and using the SEER database one may have expected nine cases.

The standardized incidence ratio suggest that this is approximately twice the number one might expect. The control findings show that only two subject experienced a malignancy exclusive of non-melanoma skin cancer.

Yet, the SEER database suggested there should have been five control subjects with malignancy. The corresponding standardized incidence ratio also reflects a smaller than expected number of malignancies among the control group.

Overall, these findings suggest the omalizumab group may have had a higher rate of malignancy than expected, while the control group had a lower rate. As noted earlier, certain publications suggest that the presence of atopy may correlate with the lower malignancy rate and the

control group data on this slide are consistent with that hypothesis.

This slides summarizes certain characteristics of the 16 omalizumab subjects with malignancies exclusive of non-melanoma skin cancer. Nine of the subjects were male and seven female. The median age was 50 at the time of diagnosis and four of the 16 diagnoses were made based upon recurrence of a previously treated cancer.

The last line notes that the median number of weeks prior to malignancy diagnosis was 24 with a range from four to 61 weeks. The rate of malignancy based upon the time interval of omalizumab exposure is shown on the next slide.

This slide shows the malignancy rate for both the omalizumab and control group both expressed in terms of events per 1,000 patient years of exposure. The exposure intervals are divided into several study time increments as shown in the first column.

In general, the omalizumab rates were consistently higher than those of control and

sustained at the higher rate over all increments of the study observation period.

This slide summarizes the cancer findings. In general, the clinical studies show that the diagnoses of malignancy was very uncommon but occurred at a higher rate among the omalizumab group than the control group, 0.5 versus 0.2 percent.

When expressed in terms of study agent exposure, the omalizumab rate was also higher than control, 6.3 versus 3.3 events per 1,000 patient years of exposure. The higher omalizumab rate was observed throughout all time intervals of the studies.

Certain comparisons using the SEER database suggested a higher than expected number of malignancies among omalizumab exposed subjects and a lower than expected number of malignancies among the control group. While these findings suggest omalizumab was associated with the higher malignancy risk, these finds are not definitive.

The confidence intervals on rate and ratio comparisons are wide such that the risk for

malignancy due to omalizumab have exposure ranges from either no increase to a considerable increase.

Next we will examine the other major serious adverse event finding anaphylaxis. Anaphylaxis was also very uncommon in the clinical study. This slide summarizes the number of cases. Anaphylaxis was recorded in four omalizumab subjects one event being temporally associated with exposure to the antibiotic levofloxacin.

Three control subjects experienced anaphylaxis, a clarification of our briefing document. One case each was temporally associated with exposure to peanuts, ceftriaxone, or an unidentified allergen. The omalizumab cases are summarized in more detail on the next slide.

In the three cases temporally associated with omalizumab exposure the onset of the reaction began one and a half to two hours following the exposure and consisted of various combinations of signs and symptoms including hives, itching, dyspnea, injection site, throat and tongue edema.

No subjects were hospitalized overnight

for the reactions and all events were managed without patient therapy. That consisted of various combinations of steroids, antihistamines, and epinephrine. In all three cases the omalizumab was discontinued.

This slide concludes the notable serious adverse event findings. Next we will begin a series of slides examining adverse events. The summary of adverse events consist of a very brief review covering three major topics. First we will examine the overall rate of events. Then examine events of special interest. Finally, we will examine the events within one subset of the study population, the geriatric population.

The adverse events of special interest include rash and three types of events that may reflect some impact of omalizumab on bone mucosal immunity, specifically digestive system events, female genito-urinary events, and bleeding related events.

This slides shows the overall rate of subjects experiencing adverse events within the

group of all control studies and the rate within the group of allergic asthma control studies. Within both groups of studies the proportions of subjects experiencing adverse events were not strikingly different between the study group, 75 versus 76 percent within all control studies and 81 versus 78 percent within the allergic asthma control studies.

Adverse events or special interest are shown on the next several slides. As shown here, the incidence of rash was higher among the omalizumab group than control, 6.5 versus 4.9 percent.

This higher omalizumab rate was observed within all grades of severity and, as noted at the bottom of the slide, the incidence of rash correlated with higher blood omalizumab concentrations. These findings suggest the somewhat higher rate within the omalizumab group was associated with the study agent exposure.

The other adverse events of special interest are cited on the next few slides not solely because of their rates, but because of the

biological plausibility that anti-IgE therapy might impact mucosal defenses. Firstly, a slightly higher rate of digestive system adverse events was noted among subjects receiving omalizumab, 19 versus 18 percent.

This slightly higher rate was due to a small excessive number of mild to moderate events such as diarrhea and abdominal pain. An interesting finding was the observation of a slightly higher rate of appendicitis within the omalizumab group, 0.2 versus 0.1 percent.

Secondly, female genito-urinary adverse events appeared at a slight excess among omalizumab exposed subjects, 11 versus 10 percent. This slightly higher rate for the omalizumab group was related to a small excess in the number of severe dysmenorrhea and severe grade urinary tract infections, as well as a broad variety of mild grade events.

The next events of special interest were the bleeding related adverse events. This comparison shows a rate of 2.5 percent for the

omalizumab group versus 1.6 for the control group. The higher omalizumab rate was related to more cases of mild to moderate grade epistaxis, menorrhagia, and hematoma formation.

This slide summarizes adverse events within the geriatric subset of the study population. Overall, this population's exposure is relatively small and includes 142 subjects exposed to omalizumab and 71 exposed to control.

These sample sizes are too small to make meaningful comparisons between the two study groups and the rates of specific types of adverse events. Consequently, the events are summarized here in terms of clusters of somewhat related events with the clusters defined by body system involvement.

A higher rate for the omalizumab group was noted for several clusters including the body as a whole event, digestive, cardiovascular, musculoskeletal, nervous, and GU reproductive system events.

This pattern of body system adverse event findings within the geriatric subset differs from

the findings within the other major age categories.

This slide summarizes the adverse event findings. The main observations are highlighted by the three major bullets. Firstly, the data show a slightly higher rate of all grades of rash severity among subjects receiving omalizumab.

Secondly, the study show the omalizumab group also had sightly higher rates of digestive system, female GU, and bleeding related adverse events, events that may relate to alter mucosal immunity.

The last bullet reiterates the comparatively higher rates of several body system clusters of adverse events among geriatric subjects receiving omalizumab. The next few slides summarize major laboratory and antibody formation findings.

This slides summarizes the laboratory findings. These findings are two-fold. More omalizumab exposed subjects in controlled had mild decreases in hemoglobin or platelet counts at some point during their clinical follow-up evaluation. For hemoglobin the difference was 73 versus 68

percent. For platelet counts the difference was 70 versus 63 percent.

Greater degrees in hemoglobin or platelet count occurred at similar rates between the study groups. It was only within these milder degrees of hemoglobin or platelet count decreases did the two groups notably differ.

This sides notes the preclinical finding that the administration of very high omalizumab dosages to monkeys was associated with the development of thrombocytopenia. These dosages were considerably in excess of those proposed for clinical use.

As shown here, the clinical studies do not suggest that the omalizumab dosages proposed for marketing are associated with thrombocytopenia. No subject with normal or high baseline platelet counts developed thrombocytopenia during omalizumab administration. Most subjects with abnormally low platelet counts at baseline had no worsening of the counts during omalizumab administration.

This slide notes that no antibody

formation was reported. However, the verification of these results is pending the review of additional data. The laboratory and antibody formation findings are summarized on this slide.

Overall, decreases of a mild magnitude in hemoglobin or platelet counts were observed among more omalizumab exposed subjects than control. The clinical studies showed no development of thrombocytopenia during omalizumab administration. Lastly, the antibody formation data are awaiting verification.

The next few slides summarize the overall safety findings. This slide highlights the major serious adverse event safety findings. As shown here, more omalizumab exposed subjects were diagnosed with malignancy than control subjects.

Specifically the absolute incidents was 0.5 versus 0.2 percent and expressed in terms of exposure, a difference of 6.3 versus 3.3 events per 1,000 patient years of exposure.

This higher rate appeared evident throughout all study exposure time periods and, as

noted in the last sub-bullet, the findings were not definitive with respect to malignancy risk in that the confidence intervals on comparisons of differences between the study groups were wide and included the possibility of no increase in the malignancy rate among omalizumab exposed subjects.

The bottom bullet on this slide notes that anaphylaxis was observed among some omalizumab exposed subjects and the events could not be attributed to any other exposure.

This slide summarizes the major adverse events safety findings. As shown at the top of this slide, all grades of rash adverse events were more common among omalizumab exposed subjects than controlled.

The middle bullet notes that omalizumab exposed subjects also had slightly higher rates of certain adverse events potentially related to altered mucosal immunity. The events involve the digestive and female GU system and various bleeding related events.

Lastly, when analyzed as system clusters

of adverse events the geriatric population exposed to omalizumab had a higher rate of multiple events.

This final slide cites the laboratory findings of more omalizumab exposed subjects experiencing a mild decrease in hemoglobin or platelet counts than control subjects at some point during the study follow-up periods. As noted at the bottom of this slide, the antibody formation data are awaiting verification.

This slides concludes our presentation of the major safety findings. I thank you for your attention and I return the podium over to Dr. Parsons. Our group would be glad to discuss or clarify any topics.

CHAIRMAN PARSONS: Thank you. Are there questions from the committee?

Dr. Atkinson.

DR. ATKINSON: I have a couple questions. First of all, I guess as far as the efficacy goes, the 24-week extension portion of the placebo controlled trials, more or less it seems like the agency is discounting it for considerations of

efficacy.

It seems like certain values should be able to be considered such as pulmonary functions which would be less liable to be influenced by bias. Have you been able to look at that data?

DR. KAISER: I think it might be unfair to say that we're discounting it. We did mention that the exacerbation data were consistent through the entire duration of observation which was out to the end of the extension period. The intertreatment group differences and pulmonary function were inconsequential.

DR. ATKINSON: I couldn't tell whether that included that data. The other question that I have has to do with the meningococcal sepsis that was observed, whether you had any additional patient information demographics and so forth, and whether this might have been a high-risk group such as a college student or something like that.

DR. RIEVES: There is additional information, I think, on that within the briefing document just off the bat. Assessing some causality

association between the meningococcal sepsis and the study drug was very difficult. The deaths are summarized within the back of the briefing document, as I recall. This was a younger individual, as I recall. The sponsor probably has it on the tip of their tongue to tell the exact age.

DR. JOHNSON: So this was a young man who was actually on a business trip to Montreal, Quebec where there was an outbreak of meningococcal septicemia and developed symptoms on return home.

Unfortunately, the meningococcal septicemia wasn't picked up quite as soon as it might have been because he was outside of the area of the outbreak. The investigator did not attribute causality to the omalizumab in this particular case. Is that sufficient information for you?

CHAIRMAN PARSONS: Thank you.

Dr. Apter.

DR. APTER: In the exploratory analysis using the SEER comparison for malignancy, you selected a subset of SEER patients. I presume you matched by age other co-morbidities, gender, things

like that. Could you tell me a little more about that?

DR. RIEVES: I wish I could. That is actually a relatively complicated analysis that was performed by the sponsor that was submitted to us. I am sure they could tell us much more detail about how that analyses was performed, the adjustments and methodology.

DR. TARONE: Okay. Here is the slide showing the results of the standardized incidence ratio analysis. I would actually like to make a couple of points. The most important point is the difference between this standardized incidence ratio and this standardized incidence ratio. It's not a matter of opinion. This one is incorrect and this one is correct.

The SEER database collects and reports and calculates their rates only primary cancers. This top analysis included two metastases and two recurrences so they would not have been classified as primary cancers by SEER. That explains the reason for the difference between these two.

The standardized incidence ratio has proven to be very useful but it has limitations as all statistical methods do. In answer to the question of how this is done, the expected value is calculated on the basis of the cancer rates in the general population, not any subgroup.

This is the population of people and it's very closely representative of the entire United States. What you are doing is comparing the incidence of cancer in these trials to what you would have expected for men and women of the same age in the general population.

Now, epidemiologists realize that is never the correct comparison group for any specified cohort. Nonetheless, it has proven very useful in many settings and just describe a couple of the biases that can occur when it's applied to clinical trials. One of the most important ones is surveillance bias.

Obviously these patients in the trials where we see very close medical surveillance. You are guaranteed that you're going to telescope some

cancer cases into the trial period that without the trial would have been diagnosed in the future.

The bladder cancer case is an example. That case was diagnosed because the patient entered the trial. There's always going to be a positive bias when you apply standardized incidence ratios to clinical trial data.

The same is true of -- Dr. Dores is aware of this -- when you look at second cancers people who have had one cancer are followed more intensely. But, nonetheless, in a study of second cancers SIRs have proven very useful.

To be fair there are some biases that work in the other direction. In this cohort the exclusion of current smokers would lead to a negative bias. Past smokers were included. Current smokers were not.

Twenty percent of the population, and you can assume that is true of SEER, would have been current smokers during the late '90s. That will lead to some kind of a negative bias. These patients were more obese than the general

population.

That's another positive bias. Even though these expected values in the SEER comparison group is never completely appropriate, it still gives you a good idea of whether you have really excessive rates either in the positive or in the negative direction.

CHAIRMAN PARSONS: Thank you.

Dr. Fink had a question.

DR. FINK: The majority of my question was answered. I was going to ask if smokers were included in SEER because obviously that would lower the expected incidence if you took smokers out and would make the data potentially not contain one within its confidence interval.

It's also, I guess, of some concern if you look at the exclusion of smokers from these trials that there is some indication that the reported malignancies with study drug are current in the same organs where you would expect to see smoking related effects because of excretion of metabolites of cigarette smoke.

CHAIRMAN PARSONS: Dr. Schatz had a question.

DR. SCHATZ: A couple of questions. One issue again is the issue of who is going to benefit and patients with FEV1 in pooled studies greater than 80 percent not benefitting. But I'm confused as to what studies were pooled because, at least as I understand it, 008 and 009 didn't include patients with FEV1s greater than 80 percent. I was wondering if that could be clarified.

DR. KAISER: I think sometimes patients get into studies outside the enrollment criteria.

DR. SCHATZ: So actually the pooled studies were those studies even though they weren't the enrollment criteria.

DR. KAISER: 008 and 009.

DR. SCHATZ: Then my second question, again I think you make the important point that there was no data on skin test negative patients but there apparently were skin test negative patients in ALTO. I wondered if anybody had looked to see whether there are any response difference in those

in ALTO who had skin tests positive versus skin tests negative?

DR. KAISER: I would actually like Genentech to answer that.

DR. JOHNSON: So if I may clarify that first question also regarding the FEV1 data, we require patients to have an FEV1 between 40 and 80 percent during the screening period. If they remain symptomatic but had improved their pulmonary function to greater than 80 percent at randomization, they were allowed to continue in the study. That accounted for the 20 percent of patients in those studies. I apologize for that.

The second part of the question is during this ALTO study we actually looked at whether or not patients had reported positive or negative skin tests and, again, during the rate ratio analysis so if there were 636 patients who had no report of a positive skin test, what you see is that there is a reduction in exacerbations in that group which is similar to the exacerbation reduction in this group.

Somewhere in the middle of -- well,

actually a slight reduction but with one or two positive allergens in those patients. The conclusion that we would draw from these data is that documentation of positive skin tests is not required to demonstrate efficacy in this subgroup. Again, the caveats apply to this controlled but open-label study.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: The patients who were noted to have thrombocytopenia and anemia, were they followed over time? Is there any information about whether these abnormalities persisted or there were lab errors?

DR. RIEVES: The decreases were very mild. As I recall, in most of the subjects, they trained it back towards normal. The analyses that I show up there are shift analyses that show a decrease at any time point. Most of them tended to return closer to normal. They were not associated -- it was either hemoglobin decrease or platelet increase. It was not associated hemoglobin and platelet increase. They were separate.

DR. APTER: I understand that.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: I had a question for Dr. Kaiser. I wondered if the sponsor could put up their slide CE-22 about the quality of life effect. That's a hard concept for me and I was just wondering how the agency decided that was not impressive, clinically important.

Maybe you don't agree with the way they are representing it where you didn't think that the quality of life differences impressed you as meaningful. I was just -- you know, I'm struggling with that and wondered why you thought that was not meaningful what they showed. That was my first question. I have another one.

DR. KAISER: The actual clinical meaning of a .5 difference in terms of what the patient is experiencing is hard to judge. The differences in the overall tests in the number of patients with those differences were not impressive.

DR. JOAD: So it's about a difference of 15 percent number of patients which was also sort of

the range of the difference in percent of patients who had reduction in exacerbations or something. Am I seeing that wrong?

DR. KAISER: I think your comparison of rates based on my reading of the graph there is probably correct.

DR. APTER: Okay. So you just think a reduction of 15 percent -- you don't disagree that .5 change in quality of life is a meaningful value?

DR. KAISER: I think the clinical meaning of that is subject to some examination. It's not clear what the meaning of a .5 difference in that is to the patient.

DR. APTER: Okay. And then my other question is just about three episodes of anaphylaxis for any drug coming through the FDA with the number of patients that were exposed, does that strike you as a lot or a little? How does that strike the agency who sees a lot of drugs, for instance, coming through?

MR. MARKS: I think that there are many drugs where we do see some episodes of anaphylaxis.

We bring that to the committee's attention because of, as you heard from Genentech in their initial presentations, it was expected that there was no potential for these sorts of reactions.

We felt it important for the committee to understand that although that may have been the belief, the data are not entirely consistent with that being the fact.

Whether or not that is the importance of those events, I think, are a matter that the agency would like to hear about and whether or not any events exist at all has a different import in this population versus other populations is a matter that would be of interest for us to hear about as well. The central point though was to ensure that the committee heard that those events have existed.

I would note that in answer to one of the previous questions about the skin test nonreactive patients in ALTO, much of the skin test information in ALTO was by history. It was not all actively tested at the time of enrollment so what their status might have been had they been actively tested

at the time of enrollment remains an open question. Whether or not all the patients described as historically negative were negative at the time of enrollment is unknown.

CHAIRMAN PARSONS: Dr. Atkinson.

DR. ATKINSON: If I may ask also along the same lines of anaphylaxis, I'm sure it's in our briefing document but could you remind me which injection these episodes occurred at? Was it the initial injection? Was it subsequent injections? It sort of has a bearing on whether the patient was sensitized to the active drug or whether or not this was some other type of reaction.

DR. RIEVES: As I recall, and I am speaking off the cuff, these were not -- for all three it was not the initial injection. There may have been one subject. Does sponsor have that on the tip of their tongue?

DR. VAN AS: We have a summary slide here. If we could show HS-4, please. As you can see from the slide, we had two patients out of the Xolair patients that had their reaction within 90 minutes

of the injection of their very first exposure to the drug which would be highly unusual for typical anaphylaxis.

One would expect prior sensitization certainly to the proteinaceous moiety of the medication. It doesn't exclude the fact that there may have been some other sort of nonspecific hypersensitivity to some of the other ingredients of the injection. We feel that this is probably not related to Xolair itself. This patient had the injection -- had a reaction 30 minutes after the fourth dose.

This is a highly unusual case because all the reactions were local at the site of the injection and they were kind of chronic and recurrent. They were not a typical picture of anaphylaxis. It was coded as an anaphylactoid reaction by the investigator.

The fourth case was the case that I described to you during the presentation of the levofloxacin ingestion which I think is an absolute typical antibiotic sensitization in anaphylaxis.

We're not convinced that there is, certainly in these two cases, strong evidence that is anaphylaxis related to the drug. Does that answer your question?

CHAIRMAN PARSONS: Dr. Atkinson had a question.

DR. ATKINSON: Yes. The first two cases in that slide were on the first exposure to the drug.

DR. VAN AS: Absolutely.

DR. ATKINSON: Okay.

CHAIRMAN PARSONS: Is it related to this slide?

Dr. Joad and then Mr. Ohye.

DR. JOAD: I'm sorry. Before we leave that slide, just a clarification because I thought the FDA said hives, itching, dyspnea, injection site, throat and tongue edema. Are you saying that is not true for those first three patients?

DR. VAN AS: In some of the patients. This patient had -- one of these patients had hives, some itching in the throat. Then a recurrence of

bronchospasm about two hours later. She was treated successfully with epinephrine, steroids, and nebulization therapy for bronchiolitis.

Then the patient is discontinued from the study after that so we had no follow-up to see in the rechallenge situation whether this would, in fact, recur again.

This patient 90 minutes after the IV infusion also had hives and some systemic effects. No cardiovascular effects and no respiratory effect at all. As Dr. Rieves had said, these cases were very easily managed and recovered very quickly.

CHAIRMAN PARSONS: Mr. Ohye, you had a question?

MR. OHYE: I had a very short question with reference to quality of life. I recall that quality of life there were gathered by a validated instrument. Is that correct? Thank you.

Oh, and one comment if I may. I think that both the agency and the sponsor have done a terrific job of presenting the data. These studies are difficult to do and difficult to interpret.

They take a long time to execute and carry out.

The discussion that we're having on the adverse reaction side, I think, is really going to give both parties a road map for discussing the labeling when you get to that later on.

CHAIRMAN PARSONS: Dr. Apter had a question.

DR. APTER: I wanted to ask of those reactions to Xolair that were called anaphylaxic if the sponsor knew how many of those patients had a history of urticaria prior to receiving the drug, referring to the slide you just put away.

DR. VAN AS: I could very quickly run through without taking too much of the committee's time on some of these patients. Could we see the slide, please? This is a young lady of 39 years old had allergies to trimenthasin, penicillin, and then had the quinlin reaction. This person had multiple allergies prior to this. The clinical picture was the typical picture, difficulty in breathing and urticaria, edema of the face and so on.

The next one. This 28-year-old lady had

multiple allergies and previous anaphylaxis associated with peanuts, chocolate, and immunotherapy. She was very vulnerable, I think, to a lot of exogenous --

DR. APTER: We know morphine causes mast cell degranulation but not allergies. Chocolate is questionable. Immunotherapy is expected. My question was did anybody have a history of urticaria prior to these events?

DR. VAN AS: Let me see the next slide, please. No. This patient nor the next one didn't have a history of urticaria beforehand.

CHAIRMAN PARSONS: Thank you. Dr. Dores had a question.

DR. DORES: Yes. I'm wondering if you could provide some background as to the reason for animal studies not being done. My particular concern is for malignancies which I think for this study has a relatively short follow-up compared to the long latency expected for cancers. In fact, the animal model may be the best way to go to assess this.

MR. MARKS: I think -- I don't believe we have our preclinical person here so I will provide the best answer I can which is that for a product of this nature where the hypothesized interaction with malignancy is not one of directly causing a malignancy, causing an alteration in a cell creating a malignant cell from a nonmalignant cell.

Rather, where it is hypothesized it is a permissive mechanism; that is, immune surveillance that may eliminate malignancies at a very early stage is where that process is impaired would seem to require animal studies.

To model that process would be very difficult. Nor is there any experience really in preclinical models of that process that we hope could reliably inform us.

Consequently, we did not have a lot of faith, as well as if we wanted to model it one might have to do very, very large numbers of animals for very long amounts of time and be left with the uncertainty of whether or not one had actually learned anything.

Consequently, the preclinical studies did not seem to be an informative way of -- a matter that would be with certainty informative. Again, the species specificity might come into play as well. This is a humanized monoclonal antibody and in other animal species antibodies against the product may well be expected which would impair the abilities for the very long studies expected. That was the first question. I'm sorry I had missed the second one. The second question was on duration of the human studies experience?

DR. DORES: That was my only question.

MR. MARKS: Okay.

CHAIRMAN PARSONS: Dr. Schatz had a question and then Dr. Swenson.

DR. SCHATZ: If I understood it correctly, 25 percent of the malignancies that did occur were considered recurrent. I wonder was there information available on history of malignancy in the entire data set so that you could look at the patients who had no history of prior malignancy and see it in the outcomes in treated versus untreated

patients if you restricted the analysis to patients with no history of malignancy?

DR. RIEVES: I think it best again that I ask the sponsor that specific question about past history of malignancy. Those subjects were allowed into the studies.

DR. JOHNSON: The specific study where patients were allowed into the study with the three-month cap on previous history of cancer was the large ALTO study. If you actually look at the patients who had that history, they were equally balanced between the control arm and the active arm. DR. SCHATZ: Well, let's see. I thought that in all of the studies they could get in with a history of malignancy as long as it hadn't been within the prior three months.

DR. JOHNSON: In the pivotal studies a history of serious illness including cancer was an exclusion criteria.

DR. SCHATZ: At anytime?

DR. JOHNSON: At anytime.

DR. SCHATZ: Okay. Thanks.

CHAIRMAN PARSONS: Dr. Swenson.

DR. SWENSON: Yes. Back to --

DR. SCHATZ: Well, then my question was if that's true, then theoretically if that information was available, then did I understand correctly that -- I can tell whether it was looked at or not but it would be of interest to me to know whether in patients who have no history of malignancy if you look at that subset do the treated versus the untreated or the treated versus controls have any difference in malignancy development?

MR. MARKS: Since these were randomized studies, although I don't have the exact rates of how many had a history or not, we expect that there was balance between the groups in terms of patients with or without a history.

DR. SCHATZ: I guess what I'm trying to get at more specifically is if one were to try to exclude the subsequent population receiving this to patients who had no history of prior malignancy, do these data suggest that, in fact, there would be no difference between treated and untreated? In other

words, that the increased risk may be eliminated if you eliminate patients with a prior history of malignancy.

MR. MARKS: I don't think we know that. We only know that it was really a minority that were recurrent malignancies.

DR. SCHATZ: Yeah, although 25 percent of 20 is still a number in terms of the differences. Okay.

CHAIRMAN PARSONS: Dr. Swenson.

DR. SWENSON: If I could return to the issue about the cancer risk. These cancers, and it's a small number, came up after the clinical studies were initiated so this issue could not have been particularly evident in your preclinical judgements.

Going back to the decision not to even pursue this in an animal model seems to me somewhat out of order. Why not consider now with these potential experiment underway to grapple with that issue?

I can't believe that there can't be some

models that might be generated now with this as a driving factor to look to see whether this antibody has some effect on tumor surveillance or on the rate of progression of tumors that might exist before clinical recognition.

DR. WEISS: I'm going to ask Dr. David to say in his involvement some of the preclinical assessments of our products to address this.

Hi. It really gets down to the point where the number of animals that were looked at in preclinical models specifically with this product were restricted because of the species cross-reactivity of the product where it is really restricted primarily to nonhuman primates. The numbers of animals that would be required with the use of this specific product would be very large and probably not feasible.

The models that are available that demonstrate increased cancer risk and, therefore, could be utilized to amplify the signal are predominately murine models where the use of this specific product would be limited because of immune

response to the product and limited exposure over the long term that would be necessary to demonstrate that effect.

The alternative approach would be to utilize a murine model, one of these amplified models. However, we wouldn't be able to utilize this specific product, but rather a homologous product that introduces yet another level of uncertainty to that sort of a study.

These are the scientific problems that we grapple with when we consider how we would design a preclinical program and what the utility of the data from that preclinical program would actually be to address the question. I don't know if I have adequately addressed your question but I have at least raised the scientific issues that we grapple with.

DR. SWENSON: Well, I think it's a question that is unanswerable at this moment but at least I have a better background on your considerations.

DR. WEISS: And could I add that when we

get to our questions to the committee this afternoon one of the questions we have forwarded to you is how to potentially better assess this risk, whether it's preclinical, whether it's developing longer-term clinical follow-up, etc. This is a very useful prelude to the questions that we want to get from you -- the answers we want to get from you this afternoon.

CHAIRMAN PARSONS: I have a question as we move on. Can somebody put this a little bit into perspective for me? I'm sure that there have been calculations made on how many patients are currently in the United States potentially eligible for this drug based on the indications requested. How large a population are we expecting are eligible for this drug? How many people?

MR. MARKS: Actually, we can't quite answer that because, as both we and Genentech have pointed out, if the population is defined as allergic asthma, it depends in part on how one defines allergic asthma. I don't believe it is well defined what population -- the size of the allergic

asthma within all of asthma is. That depends upon the criteria used.

CHAIRMAN PARSONS: Remind me what are the criteria that are currently being proposed to use as a definition for allergic asthma for labeling for this drug?

MR. MARKS: Genentech is not proposing any criteria.

CHAIRMAN PARSONS: So it's simply the term "allergic asthma."

MR. MARKS: Yes. It is our questions to the committee that we are seeking to help understand how we should go about using that term.

CHAIRMAN PARSONS: Ms. Schell had a question next.

MS. SCHELL: Yes. I guess I need a clarification. To my understanding, am I correct in understanding that the oral or IV steroids showed no benefit from this? And, if it didn't, which the more severe patients are treated with that, are there studies that increases the size of that population being looked at for the treatment of

that?

MR. MARKS: The information you are referring to is the study 011. That was oral steroid users, not IV steroid users. That study did not suggest a benefit to those patients as those patients were using oral steroids. It suggested that omalizumab did not provide a benefit.

As Genentech has mentioned, ALTO has some of those patients as well and they believe that ALTO suggest those patients could get benefit but we have concerns about drawing too heavily upon the data in ALTO.

Amongst the questions, and we have many for you this afternoon, will be whether or not we can extrapolate findings of efficacy to that population and whether or not that population warrants further study. That is really going to be answers that we're looking for from all of you.

CHAIRMAN PARSONS: We have one last question from Dr. Fink.

DR. FINK: It may be better saved for the discussion this afternoon, but just in terms of the

cancer concern, have you thought of the idea of using a preclinical trial using a murine knock-out for IgE and observing it for cancer rates where you wouldn't actually look at the actual drug but you would look at does the absence of IgE in a murine model that is well described with an IgE knock-out increase risk of tumor genesis?

MR. MARKS: I don't know that specific idea has actually been discussed and what the constraints might or might not be on that model. That's an interesting thought.

DR. ESSAYAN: Hi. Just to add a little bit to that, we have discussed it internally. Briefly, it's an interesting approach. We are a little bit hesitant that equating the physiology of an IgE knock-out to that that one might achieve with this therapeutic, that is one uncertainty that is raised.

The other is the IgE knock-outs themselves we actually discussed with several of the investigators who have worked with these mice and there have been no obvious increases or obvious

notations of cancers in these animals to date.

We're not quite sure what to make of those data because of other immunologic problems and other physiologic problems that those animals suffer from as you are well aware.

CHAIRMAN PARSONS: Thank you. That concludes this morning's session. We need to reconvene at exactly, I've been told, 1:00. As a note to the committee, there have been reservations made i the restaurant in the normal place.

(Whereupon, at 12:00 p.m. the meeting was adjourned for lunch to reconvene at 1:00 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:00 p.m.

CHAIRMAN PARSONS: We are getting ready to start the afternoon session so if everyone could take their seats. The beginning of the session will be the open public hearing. What I would also like to announce first is for committee members on the material that was placed at your place in front of you this morning, there were three additional written statements from additional public speakers.

I would like to start by thanking the members of the public who have come to speak today. Each person will come to the podium when they are announced, please. Each person has been given seven minutes to speak. The first presenter is Dr. Steven Ainbinder if he would like to come to the podium.

DR. AINBINDER: Hi. First of all, my name is Steven Ainbinder. This is my wife Ivana. It is important that she is here with me when I give you my testimony because she's really been a part of this through all of the critical subjective areas of asthma that I'm really here to tell you guys about.

I'll start by reading my testimony and then I'll make a few remarks.

Good afternoon. My name is Dr. Steven Ainbinder. I am here today from the west coast. I flew in and I want to thank all of you for giving me this opportunity to testify today on behalf of Xolair.

My comments are on my own behalf, though the Asthma and Allergy Foundation of America has helped make my presence here today possible so I appreciate that from them.

I would like to also introduce you to my wife. I frankly don't think I would be here today without her love and support to get me through this. I really mean here today.

I am 32 years old and was diagnosed as a steroid-dependent asthmatic a little over three years ago. This came very much as a surprise to me considering I did have child-induced asthma but by the time I was 14 it went away.

Then in between college and med school I actually played pro-tennis so I was actually in very

good shape prior to somehow coming down with severe asthma. I'm going to say coming down because it did come as if it was a virus out of the blue.

In August 1999 I began wheezing uncontrollably after a run and ended up in the emergency room. I was diagnosed with severe asthma. Two weeks later, I again had a severe attack this time resulting in pneumomediastinum and pneumothorax I ended up in the hospital for days, put on strong steroids, and initially started on the routine things that we all start our patients on when they are diagnosed with asthma.

Well, this didn't seem to help. Within six months from them I would be operating on my patients and have the anathesiologist come around the table, lift my mask, and give me my MDI, probably something you don't want most of your surgeons to be doing.

Well, at that point my wife had a long talk with me during one of my ER stints and said, "Maybe it's time to take a sabbatical. Let's take a month off." Well, you know, as physicians it's not

easy to take time off with our Type A personalities, but I did.

One month turned in to three months, three months turned into six months and here I am here today over three years later no longer doing what I love the most, being a clinical physician.

One thing interesting about that, I am, by the way, ob/gyn oncologist at UCLA Medical Center, and one of the privileges that gives you, as you guys know, it's not the salary, it's definitely your availability to be with the best physicians that this plant has to offer.

I was seen by the best rheumatologists, pulmonalogists, asthma physicians, endocrinologists, internists, anyone you could imagine seeing. Really unfortunately the only thing they could determine was that steroids was the only way to treat me. At that point they diagnosed me as a steroid-resistant asthmatic.

Unfortunately, I had never heard of a steroid resistant asthmatic. I didn't even know what it was. Obviously I knew what severe asthma

was but not what steroid-resistant meant. At that point I only knew that I had been on 120 to 140 milligrams of prednisone and it wasn't even showing any of the real side effects.

My asthma wasn't under control and they were trying me on everything from trylandeomyecin to considering some chemotherapeutic agents and nothing was helping. I was up every night and in the emergency room every other day including the intensive care unit at least once a month.

In August 2001, my physician recommended the randomized clinical trial for Xolair. Being a physician myself and having published some articles in immunology, I did my due diligence prior to joining the trial and was intrigued by the drug's mechanistic approach.

However, the results were incredible. Within one month of joining the trial, my Medrol medication was reduced from between 60 to 800 mg daily to about 4 mg and that was only to keep my adrenals in line.

I was never hospitalized during the six-

month trial of Xolair that I was on. Not hospitalized. I had not been in the hospital and before I had an ER visit at least three times a month if not more.

Within a month of going off of Xolair after that first trial I was ill again. I was back on my Medrol and instantaneously I was back to living the life of a debilitated severe asthmatic.

Then, in September 2002 they had an extension to the trial, which I was allowed and benefitted from again, and went another six months both objectively and subjectively clinically better, improved. Back to being part of our society. Back to feeling good.

As a patient with severe asthma, as a medical doctor, as a scientist and as a husband, I urge the FDA to approve Xolair. As a physician and scientist, my main message here today is that asthma is truly a heterogeneous disease.

We can talk, as we did today, about mild to moderate and moderate to severe and allergic versus nonallergic, but as we all discussed, there

are no definitions. What we have are people who are sick from asthma.

People who have been diagnosed with bronchial airway reactive disease which may or may not be allergic but you cannot live normal lives. For steroid-resistant asthma there is no other drug on the market, unless anyone can show me one, and Xolair is the only thing that can help us.

I would also like to say that as a patient, physician, and a caring husband, I ask that PDA approve Xolair because it is the only drug that helps me. My life depends on it. It truly does.

Thank you for letting me come. Thank you for letting me talk. Thank you for letting me listen.

There is a side note that I would like to bring up having heard all of this today. I've sat on maybe not the FDA but I've sat on some similar committees back in my days at UCLA. I remember talking about the minutiae and looking at some of the points that seemed to be critical at the moment but now having a completely different perspective.

I have to tell you this is really regarding people. This is regarding the clinical ability of people to be productive in their lives. It's easy to kind of ignore that, especially when you are doing your job, which you all are doing fabulously.

As a gynecologist, you will probably laugh, they always love to tell me, "God, you are a male gynecologist. You don't know what it's like having a pelvic exam. You don't know what it's like having ovarian cancer."

My reply would always be, "Well, I don't know what it's like having ovarian cancer. I know how to treat it." One of the things you might want to know today is just real briefly what it's like day-to-day being a severe asthmatic. This is just what I'm going to leave you with.

If I'm lucky, I only wake up once or twice during the evening to take my nebulizer of which my wife, of course, has to wake up with me because I can't breathe and she has to as she is getting the nebulizer ready for me, put on her clothes because

she doesn't know if I'm going to make it or if we're going to have to call an ambulance or dash to the ER with our portable nebulizer.

Then around 7:00 a.m. if we do make it through the night I do my daily nebulizations, my medications, take my Medrol which, by the way, doesn't taste too good, and make it through the day.

By noon we have another nebulizer. We have more medication. We have the terrible side effects of steroids which, trust me, none of the side effects you can imagine of Xolair are even remotely compounded to what it's like living day to day on Medrol. I'm sure you are all aware of that.

By the evening you count your blessings if you haven't had a severe attack during the day. You watch your food intake because you are feeling weak, yet you're so bloated you can't fit into your clothes.

Then you start another night and you wonder if and when this is ever going to end, as soon and acutely as it came on. That is really what it's like because when you can't breathe it's

holding your head under sand. It's diving under water and not knowing when you can come up.

Xolair is it. It's the only thing that has helped me. I would like to thank the people from Genentech for coming up with such a wonderful medication. Thank you very much.

CHAIRMAN PARSONS: Thank you very much.

The next speaker is Ms. Sandra Fusco-Walker who will come to the podium.

MS. FUSCO-WALKER: Good afternoon. My name is Sandra Fusco-Walker and I'm the mother of three young adults who have grown up dealing with asthma and allergies. I want to thank you all for the opportunity to speak here today.

I've been a volunteer with the Allergy and Asthma Network, Mothers of Asthmatics. I have now joined the organization. I am an outreach education coordinator. AANMA is a nonprofit, patient education, and advocacy organization. Our mission is the dedication to eliminating death and suffering due to allergies and asthma.

Neither AANMA nor myself has a financial

interest in the companies represented in this issue. AANMA pays my salary and they have covered my expenses to come here today. I live in New Jersey.

AANMA is supported by family and medical professional donations and restricted and unrestricted federal and pharmaceutical grants including the companies represented here today. I am here to represent the organization's views.

Historically improvements in asthma treatment have come in increments for which patients and their families are eternally grateful. Xolair represents the first biologic for the treatment of asthma, a gigantic leap from traditional molecular therapies.

Over the last few years we at AANMA have been following the research on Xolair. We've answered patient question. We get about 125,000 hits a month between our phones and our e-mail at our website. The questions are, "When is Xolair going to be available? What does it do? How does it work? Is it a cure? Will it mean I can get a dog? How much is it going to cost and will my

insurance cover it?"

Teaching families about Xolair is an opportunity to teach about the human immune system and the importance of ongoing proactive medical care. AANMA does not view Xolair as shotgun therapy or a reason to abandon effective asthma treatment such as allergen avoidance, immunotherapy, inhaled corticosteroids, bronchodilators, and other medications patients use.

Instead, we view Xolair as an important new option for treatment that, once available, will liberate adolescents and adults whose asthma defies existing therapies. While patients trust the FDA to look at Xolair from a safety and efficacy viewpoint, patient are hoping that Xolair, and access to Xolair, will unshackle their lives and remove the ever present weight and unpredictability of asthma.

Thank you very much.

CHAIRMAN PARSONS: Thank you very much.

The next speaker is Ms. Jennifer Merenda.

MS. MERENDA: Good afternoon. Thank you for allowing me to come here today. It's a very

important issue. I'm just happy to testify before the committee.

Again, my name is Jennifer Merenda. I'm a registered nurse with the R. Adams Kelly Shock/Trauma Center in Baltimore, Maryland. I'm also a wife, a mother of two children, one of which has asthma as well.

My comments today are on my own behalf and on behalf of my won. The Asthma and Allergy foundation of America has helped me make my presence here today possible.

I've been waiting three years to tell my story. Since birth I've had restricted airway problems. I spent the first two weeks of my life in the hospital because of breathing difficulties.

I spent most of my early childhood years restricted in my activities, as medication to treat my chronic symptoms was not available. Instead, avoidance was supposed to be the best treatment, which was good in theory but was not practical in real life, especially for a child.

I awakened many nights suffering with

shortness of breath and made frequent retreats to my parents' room for assistance. I spent every Wednesday afternoon and every Saturday morning in my doctor's office for a minimum of one and a half hours while I received my allergy serum injection.

I endured tenderness and swelling at the site that resembled an egg beneath the skin surface. Winter nights were spent in my bedroom with a vaporizer and frequent chest physiotherapy. I would be sent home from school because I "looked" like I was having too much trouble breathing, even as I pleaded to stay.

I stopped allergy injections in my early teens as there did not seem to be any real benefit. I began to use Primatine Mist as that was the most useful over-the-counter medication at the time. I grew tired of the doctor's office.

As I grew into my late teens my breathing and allergies worsened. I was tired of medicine. I was tired of reading every food label. I was always taught to deal with my health problems and not use asthma as an excuse. I did not want sympathy from

anyone. I would rather enjoy life, wheeze, take my inhaler and move on. I guess that was part of being a teen.

At the age of 17, I finally realized that my asthma was not controlled. I began my allergy injections again and was prescribed Theopholine twice a day with Ventolin for breakthrough wheezing. While both drugs certainly helped my asthma, I experienced several side effects.

Eventually I changed to a sustained release form of the Theopholine and had more control, but again, not without the side effects. Along came Serevent, and though I continued to have my problems, I felt it was under control. Little did I know what control could be, however, until a friend of mine with asthma told me about a new clinical trial.

When I joined the Xolair trial I was told the drug being tested was not yet approved by the PDA, but that if I got the drug instead of placebo, I would most certainly see improvement. Truth is, I didn't feel like I had

anything to lose and my expectations were quite low. To qualify for the trial, I had to stop current medications. This was the most difficult part, as I had to restrict my activities because of shortness of breath. I couldn't even walk a flight of stairs.

I can't emphasize enough for you my surprise with this miracle injection I began to receive. I did not experience any local effects at the injection site and my asthma symptoms were completely alleviated.

While I received the Xolair injections, I experienced the life of a normal person. I say this because prior to Xolair, people in my life would say "you're breathing heavy again" or "I can hear you coming around the corner before I see you."

With Xolair, I stopped clearing my throat and coughing frequently. I could go anywhere without the fear of losing my inhaler. I was no longer concerned about needing to have an inhaler in every coat, in every pair of pants, in my car, or in a relative's home.

I was not afraid to go on vacation and be

without a nebulizer machine. I did not make noise breathing. I slept quietly. I did not walk around with my mouth open. I did not have to worry about restrictive clothing on my chest.

My nose worked and was no longer what I refer to as "purely cosmetic...serving no function." I was truly free. For the first time in my life, I felt like everyone else did not have his or her "eyes of concern" focused on me.

I told you in the beginning that I've waited three long years to tell you my story. That's because when the Xolair clinical trial ended three years ago, I immediately returned to a life of daily asthmatic symptoms. I felt I had something great and now it's gone.

I am a registered nurse. I work in a center that is known worldwide. I continue to praise this miracle drug to physicians and colleagues that I work with daily. I field questions from other patients about the drug that once relieved me from the misery of my asthma.

And as a nurse, I'll be the first to say

that prevention is where health care starts. Prevention is what Xolair is all about as far as I'm concerned. The fact is, it is difficult for patients to understand why a drug that has demonstrated so much promise has not been approved yet.

I continue to be asked by my colleagues, and by my family and friends, about where the drug is currently in the approval process. I not only think of myself though. I think about how many emergency room visits for people with asthma could be eliminated.

I think of my son and the potential for his life to be free from continuous medication and constant fear. I look to the future and hope that many more people with asthma will know what it means to lead a normal life.

I sincerely believe Xolair can provide that freedom. I urge you today to recommend that this drug be approved. Again, thank you for your time and for allowing me to share my story.

CHAIRMAN PARSONS: Thank you very much.

The next speaker is Dr. Stuart Stoloff.

DR. STOLOFF: Madam Chairperson, Members of the Committee, my name is Dr. Stuart Stoloff. I am a Clinical Professor in the Department of Family and Community Medicine of the University of Nevada School of Medicine.

In addition, I am a Member of both the Expert Panel II of the NHLBI "Guidelines for the Diagnosis and Management of Asthma" and the NIH, NHLBI Science Based Committee for Monitoring World Asthma Research Literature.

I very much appreciate the opportunity to share my perspectives on issues of importance to your consideration of the approvability of Xolair for the treatment of moderate to severe asthma.

From the outset, I want to make it clear that I am not here to advocate a specific position on whether this particular agent should be approved or not, but to highlight the significant need for an accurate diagnosis before such drugs are administered.

Furthermore, I would like to note that any drug that can reduce the symptoms of moderate to

severe asthma and improve patient functioning and well-being are greatly welcomed.

For the record, I would like to state that I have no conflicts with respect to the approvability of Xolair. I neither own stock in Genentech or its competitors, nor do I consult for them.

My appearance today, however, has been supported by Pharmacia Diagnostics, which markets a highly specific PDA approved in vitro diagnostic test that allows physicians to accurately assess a patient's sensitivity to a specific allergen to tailor therapy appropriately.

As is clear to this Committee, asthma is a disease of staggering proportions, affecting over 26 million Americans and having significant individual and societal impact, and alarmingly, the prevalence of this disease is increasing.

Unfortunately, as identified in numerous studies, asthma morbidity and severity disproportionately affects socially disadvantaged populations, including African Americans and

residents of low-income inner-city neighborhoods.

This reality highlights the importance of cost effective strategies for reducing the burden of this disease, and the need for identifying those who could benefit from costly therapeutic intervention before their initiation.

Asthma is a multi-factorial disease with numerous triggers. The association of asthma and allergy has long been recognized. Inhaled allergens, such as pet dander, dust mites, cockroach allergens, molds and pollens, to which a patient is sensitive, are known to increase asthma symptoms and severity and to precipitate asthma exacerbations.

Demonstrating a patient's relevant sensitivity to inhalant allergens will guide the clinician in implementing therapeutic interventions, including the recommendation of specific environmental controls to reduce exposures.

In July of 1997, the National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI) published Guidelines for the Diagnosis and Management of Asthma. I had the honor of serving on

the expert panel that promulgated these guidelines, as well as the panel that updated these guidelines last year.

Importantly, the clinical practice guidelines specifically note that for at least those patients with persistent asthma on daily medications, the clinician should:

1. Identify allergen exposures

2. Use the patient's history to assess sensitivity to seasonal allergens

3. Use skin testing or in vitro testing to assess sensitivity to perennial indoor allergens

4. Assess the significance of positive tests in the context of patient's medical history

The Guidelines also specify the importance of an accurate diagnosis, as many conditions present with similar symptoms. For instance non-allergic symptoms that present as allergy, such as rhinitis, sinusitis and gastrointestinal reflux should be ruled out and managed appropriately.

Unfortunately, today, almost 7 years since the guidelines were published, their implementation

remains woefully inadequate. This lack of adherence to the Guidelines relates to the under diagnosis of the severity of the condition, and hence the perceived need for testing, the difficulty in obtaining a referral to a specialist and the perception that allergy testing is difficult to do.

It is also likely that patients seeking a "quick fix" are enamored by the promise of new pharmacotherapeutic approaches, and as such are not even aware that avoidance of the agent they are sensitive to may be the best therapeutic approach.

Primary Care Physicians manage over 65 percent of allergy and asthma in the US and often do so with minimal objective evidence of underlying etiology. Only a very small, single-digit percentage, of allergy patients seen by such physicians are actually tested for allergen-specific IgE antibodies, resulting in many being misdiagnosed and therefore mistreated.

A proper work-up, including allergy testing, will not only enhance diagnostic certainty, and determine appropriate management, but will have

significant cost saving advantages as well. This is particularly relevant for a drug that is expected to cost patients and providers over $10,000 per year.

It is my belief that it is imperative for all patients to have an appropriate work-up, including allergy testing before consideration of initiation of Xolair, or other drugs for managing patients with moderate to severe asthma because there may be factors that can be treated that could diminish the need for such treatment. Conversely, such an evaluation could identify patients who could best benefit from treatment.

Both allergy skin testing and allergy blood tests are equally reliable in determining sensitivity and one or the other of these approaches should therefore be routinely Xolair Advisory Committee employed when evaluating patients with persistent asthma.

The choice as to which diagnostic test to use should be based on the clinical setting and abilities of the treating physician. In the primary care setting, the necessity for training on both the

procedure and interpretation of the result will in most cases preclude primary care physicians from performing skin testing.

In vitro testing does not require knowledge of the "art" of skin testing, does not require availability of allergen extracts, can be performed on patients who are taking allergy medications or who have eczema, and is not associated with systemic reactions or increased risks.

There is increasing evidence that there is a significant under classification of asthma disease severity by treating physicians, which may in part, underlie why testing is not occurring to the extent it should. A study published this year by Wolfenden, et al in the January 2003 issue of the Archives of Internal Medicine demonstrates the significance of physician under estimates of underlying disease severity on treatment outcomes. It found that regardless of the physician group, patients' perception of disease severity was greater than that of the physician, resulting in asthma care

that was inconsistent with national guidelines and associated with poor patient outcomes, including underutilization of effective measures and more frequent ER visits and hospitalizations.

Halterman and colleagues published findings of an underestimation of asthma severity among urban children with asthma. This study published in February, 2002, in the Archives of Pediatric and Adolescent Medicine, found that only one-third of children in the sample received the recommended daily therapy for their level of asthma severity.

Many have postulated that difficulties experienced by both patients and physicians in recognizing asthma severity and subsequent under treatment may be a reason for the high level of asthma burden in this country.

This is best exemplified by the finding of Fuhlbrigge, et al in a recent publication in the American Journal of Respiratory and Critical Care Medicine (Oct. 2002) that found that when patients are appropriately classified, over 70% of patients

have moderate to severe persistent asthma.

The fact that many of these patients were considered by their physician to have mild intermittent asthma resulted in the failure of appropriate treatment modalities to be instituted. I am concerned, that as new therapeutic approaches, such as Xolair, are approved that patients and physicians will view them as a panacea.

This will result in many more patients being treated with pharmacologic approaches without an adequate diagnostic work up. This will not only potentially expose them to unneeded therapies, but also prevent them from having the necessary knowledge to practice avoidance.

I think this is particularly important for an agent with an anti IgE mechanism, as many will think that it adequately addresses symptoms of an allergic nature. Such an outcome, I fear would further enhance the underdiagnosis and mistreatment that is rampant in asthma care.

I would encourage the Committee to consider that the labeling for Xolair stipulate that

diagnostic evidence of an allergic (IgE) etiology be established if this therapy is to be appropriately initiated.

The routine utilization of diagnostic testing in evaluating patients with persistent asthma would identify the appropriateness of treatment for the patient and diminish symptoms.

Improving the diagnosis and classification of asthma severity will improve patient outcomes and have a positive effect on overall public health.

Enhancing the ability of the primary care physician to effectively assess whether an allergic etiology underlies a patient's asthma symptoms should help to ensure the rational selection of therapeutic modalities and result in improvement in quality of life for both the patient and their family.

I appreciate that opportunity to offer these comments and would be happy to answer any questions you might have.

CHAIRMAN PARSONS: Thank you very much.

The next speaker is Mr. Ted Vallejos.

MR. VALLEJOS: Hello, my name is Ted Vallejos. Thank you for taking the time to listen to me. I am here today with the help of the Asthma and Allergy Foundation of America, but my comments are on my own behalf. I hope that after listening to my history and experience with Xolair, this will help you make the decision to approve this new and amazing medicine.

Throughout my adult life and the majority of my childhood, I have never experienced the freedom from asthma that I did for the short time I was on Xolair. At the age of 7, I aspirated a silver tip of one of those old, black government/military pens and my life with asthma began.

Since then, I have had ER visit after ER visit and hospital admission after hospital admission. My medical chart is the size of a large phone book. At the age of 13, my doctor told my parents that due to my asthma, we had to leave Hawaii. Of course, my brothers and sisters were not very happy.

I'm currently 38 years old, married, living in San Diego, and working as a Respiratory Therapist. The move to San Diego definitely decreased my ER visits and hospital admissions.

From the ages of 7 to 24, I was admitted to the hospital about seven or eight times. In 1989 at the age of 25 I was intubated for the first time. I was again intubated in 1991. Another ICU admission followed a year later.

In 1994, a co-worker recommended I consult with Dr. Eli Meltzer who helped me gain control of my asthma. I have not been intubated, hospitalized, or gone to the ER since, but I always had to worry about wheezing and shortness of breath.

Prior to seeing Dr. Meltzer in '94,1 was wheezing daily and awakening almost every night from my asthma attacks. I had to sleep with a nebulizer at my bedside. My upper airway was always mildly stuffy.

My medications included Uniphyl 1200mg QD, Azmacort 4 puffs BID, Intal 4 puffs BID, using my albuterol inhaler 6-16 times a day (about a canister

a month), and Prednisone bursts about 4-6 times a year.

Dr Meltzer changed my regimen to albuterol nebulizers BID, Serevent BID, Uniphyl 1200mg QD, Aerobid 4 puffs BID (now on 4 puffs Flovent 220mc), albuterol MDI PRN, 20mg Prednisone QD (for about 4 months then changed to QOD), and Claritin (but now Allegra).

This new regimen helped reduce my wheezing and cut my prednisone bursts to once or twice a year. For almost two years I tried allergy-desensitizing shots with no success. I could not get out of the first phase because my wheezing would flare up.

I have also been taking Prilosec for my stomach pains and gastric reflux. I have tried Accolate (and now Singulair). Singulair has helped my symptoms a little and I have been weaned from my prednisone dose from 20mg QOD to about lOmg QOD.

Approximately two summers ago, I volunteered for the Xolair clinical research study. By the middle of the trial, I was feeling and

breathing really well. My wheezing would rarely flare up and my nose was not as stuffy.

In fact, by the end of the trial I was exercising on a regular basis. My breathing was so strong I started jogging. Until that time, I had never been able to run continuously for more than a mile in my 38 years.

Fortunately, I was able to receive Xolair for an additional three months after the trial. During that time, I was able to take myself off of Prednisone and the 1200mg of UniphyL I was also able to decrease my Flovent usage from 4 to 2-3 puffs each day.

My PFTs showed improvement-my FVC increased from the mid 80s to the mid 90s, my FEV) went from the mid 60s to the mid 70s, and my FEF25-75 increased from the low to mid 30s to the mid 40s.

My IgE blood level had dropped.

It was the best I had felt in a long, long time. I ran my first 5k run without stopping to walk. A month later, I ran another. It was amazing. I had my

inhaler with me, but didn't need to use it.

During the last two months on Xolair and even for a couple of months after, I was able to leave the house without my inhaler in my pocket. This was something I had never experienced before! Never in my life did I think I could leave home without it!

Unfortunately, it has been a little over a year since my last injection of Xolair. My asthma, wheezing, shortness of breath, stuffy nose, and having to have an inhaler in my pocket at all times has gradually returned. I actually still feel better than I did prior to the study.

In fact, although I had never been able to participate directly in sports growing up, thanks to the benefits of Xolair I joined a softball team. My team is 7 and 1 and heading into the playoffs and I'm actually missing a game to be here with you today.

I'm currently in the middle of my second softball season and it is getting more difficult to run those bases. I tighten up very easily. I can no

longer jog or run for pleasure. And, although I'm still off the prednisone, I'm back to 4 puffs of the Flovent, back on a little bit of Uniphyl (400mg), and Allegra (these along with the others I mentioned earlier-Singulair, Serevent, and Prilosec).

Another nice thing about Xolair was that it didn't give me the typical side effects like tremors, like the feeling of your heart pounding out of your chest, stomach pains, nausea, hunger, feeling tired, or my face looking like a moon (just to mention a few).

I believe that if I could continue with Xolair, I could maybe get by with only the maintenance drugs Flovent and Serevent. Perhaps someday I might get by with just Xolair. I'm not sure. But I am sure that I could definitely live the rest of my life free of asthma if Xolair was approved.

I thank you very much for your time to listen to me.

CHAIRMAN PARSONS: Thank you very much. Thanks to all of the speakers today. I would also

like to ask if there is anybody in the audience that would like to speak today. If there is anybody, we would ask that those comments be limited to three minutes.

If there is no one else, then again I would like to thank the speakers today and also the three people who submitted written testimonies on the behalf of the drug. We are going to move now into the next section of the meeting which is for the committee members to specifically address the 10 questions that the FDA has asked them to evaluate and consider.

I would like to just preface the beginning of this discussion to say there are indeed 10 questions that are fairly extensive that the FDA would like some discussion and consideration on.

What the plan is is we will discuss each of these, develop potentially some consensus comments but that only the last one, No. 10, will be take a formal vote. Often times we vote on multiple questions and this plan is to be voted only on question No. 10.

I'm going to start the discussion by reading the first question and then we will open it up for committee discussion. The first question we are requested to consider is states:

1) The table below indicates the results from the four randomized, placebo-controlled, double-blinded studied of subcutaneous omalizumab in allergic asthma submitted by Genentech. The results are summarized by the analysis of the percentage of patients with at least one exacerbation. The table is presented in your packets.

Additional studies in allergic asthma patients include a phase 2 intravenous study, and two controlled but open label trials designed primarily for safety assessments.

Other endpoint variably reached nominal statistical significance, but for many of these endpoints the differences between groups was of uncertain clinical meaning.

The two specific questions are:

a) Please discuss the exacerbation results with attention to whether they provide

substantial evidence of meaningful efficacy of omalizumab.

b) Do any of the other endpoints strength the efficacy findings? If so, which specific ones?

Now, what I would like to have the committee note is many of the next nine questions actually address fairly specific points that relate to this general point. We'll start the conversation with this more general open discussion and then we'll go to some of the specifics and move forward. I will open it up to the first question. Comments?

Dr. Fink.

DR. FINK: Clearly, time to exacerbation has been used as a fairly standard measure of efficacy in asthma trials. More importantly, drugs that show improvement in pulmonary function but don't prevent flairups do little to impact upon the cost or the mortality of asthma. I think ascerbation rates has generally become regarded as one of the more stable and one of the more important endpoint measures for asthma trials.

CHAIRMAN PARSONS: Additional comments from other members of the committee? Do other members have specific comments regarding other endpoints and how they either strengthen the efficacy findings?

Dr. Schatz.

DR. SCHATZ: Well, I think actually most of the other endpoints looked at in most of the trials would be supportive. Particularly steroid reduction is something that is medication sparing. That is useful, particularly in the case of not showing an increase in rescue therapy, for example, and quality of life.

Granted, there could be some question as to whether .5 is or isn't significant, but I think most people feel that is meaningful and, therefore, I think the quality of life change is in the same direction as a very important patient-centered outcome is supportive.

CHAIRMAN PARSONS: Additional comments?

Dr. Atkinson.

DR. ATKINSON: If I can turn my mike on.

I would just like to make a comment that it seems that there must be -- we're using IgE and sort of vague definition of allergic asthma which everybody, I guess, would agree has not been well defined as sort of the indication that this drug may be effective.

It seems that there may have been a very wide variation in the trials that were done. Some people from the testimony today apparently got tremendous benefit and other people presumably receiving none.

Some people even discontinuing treatment so there may be a wide amount of response and we may actually not know who is going to respond very well until they are placed on a clinical trial basically of the medication.

CHAIRMAN PARSONS: And I would like to comment and ask other committee members for their opinion regarding although the exacerbation results appear by many to be significant, it appears to be for a fairly select patient population. Do other people have comments on that?

That relates to the next question we're going. In terms of is there meaningful efficacy, how does this relate to the patient population studies and is it potentially extractable to others?

Dr. Fink.

DR. FINK: I don't know that you can extrapolate it safety to other populations. I am particularly concerned about the exclusion of any trials looking at smokers. A large number of them were severe adult asthmatics that smoke and it's just a reality of life. Exclusion of them provides us with no data as to whether this drug would be more or less effective in that group.

One could also question the issue of the overlap, at least in clinical care, of chronic obstructive pulmonary disease and asthma. There is no data to bear upon that issue which is, again, another large population of people who might or might not be exposed to this drug. There it would be critically important if their COPD have an allergic component or not.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: Well, with regard to the proposed indication, I would think that the allergic asthma does need to be defined according to the group that was studied, which means at least one test, skin test or in vitro test, looking at true allergy, that should be part of it.

Then the other group I'm uncomfortable with is the group over 65 which I think will come up in the safety part also. It's too small a group. It didn't show that much efficacy and then there will be side effect concerns.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: I would just like to echo you. You certainly can't extrapolate this to a group of patients who have characteristics totally different than those who were studied and that is the case when it comes to specific IgE.

Considering the presumed mechanism of this drug it's an additional reason why I would certainly not want to extrapolate this to patients who don't have demonstrable specific IgE to perennial antigens.

CHAIRMAN PARSONS: As a group before we go on to question two, I think it would probably be helpful for the FDA if we could sort of give our individual opinions. Not a vote yes or no but just generically do we overall feel that there has been demonstration of meaningful efficacy of this drug in the patient population tried.

MR. MARKS: Actually, before you go on to that, I would like to ask for a little bit more discussion or advice drawing upon comments of Dr. Schatz and an earlier one of Dr. Joad.

On the Juniper AQLQ to understand how you think about that, as was shown on the Genentech slide, there was a difference in the percentage of people who achieved a .5 change and that was different between the two groups.

However, the mean or median between the two groups overall, that difference was on the order of a quarter point. I would like perhaps a couple of comments to understand how you think about the difference between looking at the two groups overall and focusing upon the percentage who hit a criterion

change.

CHAIRMAN PARSONS: Does somebody want to speak to that specifically?

DR. SCHATZ: Well, I mean, I just would point out that, and, again, I'm not a psychometrician, but I think that the way that instrument has been validated, I think one can have confidence in that as a substantial change. Looking at individual patients compared to themselves in a situation like that, I think, is inherently meaningful as opposed to means that may miss individual changes.

I guess the combination of the fact that I'm comfortable with that as a significant change based on the validity type testing that's been done, and the idea that that involves an individual patient who has made a significant change makes me comfortable with that.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: I agree with Dr. Schatz. I'm not concerned with the use of the AQLQ in that it shows a change. I'm not concerned that

exacerbations change. I'm most concerned about the imprecision of the population studied the difficulty of identifying what's allergic. The older patients who have not been -- there is no experience and who, by the way, are frequently not allergic.

CHAIRMAN PARSONS: Does anybody on the committee have anymore comments regarding the initial efficacy measurement which is specifically the decreasing exacerbations in terms of the relative percentage change between the groups in the studies? Do people feel that was a strength?

Dr. Joad.

DR. JOAD: I just would like to make the comment that that I'm not sure I felt that the study used state of the art management of exacerbation based on what I said earlier about a clear action plan that could be easily instituted early in exacerbations.

So I do feel that it shows efficacy in the situation in which it was used. Whether it is really better than the national, then very good institution of what we should be doing according to

the national guidelines we don't know and we probably won't know.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: Just, I guess, a perspective comment that if one looks at the reduction in exacerbation rates, the relatively modest improvement in FEV2, and the changes in the quality of life scores, they are similar to or superior to some of the other drugs that we currently consider our mainstay of asthma treatment.

Many inhaled corticosteroid trials have had difficult showing a .5 change in quality of life scores. I think in comparison to currently used drugs the data presented here is actually fairly robust and fairly comparable to drugs we all feel comfortable as called mainstays of asthma treatment.

CHAIRMAN PARSONS: Other additional comments regarding the efficacy measurements that were performed?

Dr. Chinchilli.

DR. CHINCHILLI: Yes. I just wanted to ask the clinicians on the panel if they are

satisfied with the FEV1 improvement since it is modest, or is that just pushed aside because the improvements in the exacerbation rates are important?

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: I have another comment later but that dampens my enthusiasm.

CHAIRMAN PARSONS: Dr. Schatz, you had an answer to that question?

DR. SCHATZ: On the other hand, there is quite a bit of information where studies have tried to evaluate measures of asthma control, particularly symptom oriented and other things and FEV1. There is often not a very good correlation. I think it has to do with a couple of things. It has to do with fixed instruction that can lead to changes in clinical status that just don't get measured in FEV1.

It has to do with FEV1s being measured as percent predicted but you would never know what that is, really what is optimal for that individual patient. I'm less concerned about that because I

believe that good asthma control measures don't always correlate as well with FEV1.

CHAIRMAN PARSONS: Dr. Apter, you had another question?

DR. APTER: I was going back to another point, the concern that the patients that were tested might have had positive tests to cats and dogs but we weren't presented with any data about exposure to those allergens and about change in asthma parameters with continued exposure. I think this data is important for understanding if this is a drug that can address true allergy.

CHAIRMAN PARSONS: Dr. Swenson.

DR. SWENSON: Well, with regard to the meaning of the efficacy results, I'm a little bit disappointed that these are not as great as we all would have hoped on the mean despite some moving stories here for individuals that have benefitted tremendously.

The lack of use of other control or medications in the big studies leads me to think that if anything had those therapies been part of

their standard therapy the results might not have been as impressive as were presented here. It made a strong case for the compound than might really truly exist out in the real world.

CHAIRMAN PARSONS: I actually had similar concerns regarding that. Indeed, if patients had been on what has been discussed here as sort of standard treatment, if that had been the primary arm that was being compared to, that indeed the actual differences seen may not have been quite as large. I think without doing a trial comparing those two groups it would be hard to say for sure but I had similar concerns.

Are there other comments regarding question No. 1 or were there other specific features of question No. 1 you want to discuss before we moved on?

Dr. Joad.

DR. JOAD: I was just going to ask Dr. Chinchilli the question about the quality of life results. The fact that you can show a big statistical significance using fixed change and

percentage of patients who have that fixed change versus a mean change, to me it means that there is a variable response. Some people responded very well and other people may not. You lose it because of the mean issue.

DR. CHINCHILLI: Yeah. Well, that can work both ways. That can work in your favor or can work against you. Since the data weren't presented with the means, I'm not sure what happens in this particular case.

MR. MARKS: Actually, when the means are calculated those do hit nominal statistical significance very well as well. These were pretty well-sized studies for those types of tools and there is definitely a statistical significant difference. Our questions are regarding how meaningful are the differences in terms of how you view them.

DR. CHINCHILLI: So it was significant both ways?

MR. MARKS: Yes. The statistics were significant in any manner of looking at them.

DR. JOAD: My point is that we thought that a 15 percent -- when 15 percent of the people had less exacerbations, we thought that was robust. But when 15 percent have a decrease of .5 on the quality of life, we are wondering whether it's robust or even matters.

I think somehow it comes out in statistics or something when the mean changes less than the .5. That is, the difference in the means is less than .5 which is the clinically important difference on that scale.

CHAIRMAN PARSONS: I think part of the issue may be -- I'm not speaking for everybody but I think part of it is a 15 percent change sounds meaningful but what has changed? One was an exacerbation rate that I think most people around the table have decided is a meaningful change.

The question is is 15 percent change -- the next 15 percent change is a change of .5 on a scale. The question is is a change of .5 on a scale a real change. I think that was the question to the committee.

If it is considered a real change, then a 15 percent change between two groups -- do you see what I'm saying -- makes a big difference. So the question that came out to people, and people have commented that a change of .5 on that scale they felt was significant. Is that correct? Does that help clarify the issue as to what the --

DR. JOAD: Minimally significant.

CHAIRMAN PARSONS: So a change of .5 if considered minimally significant. Okay.

Dr. Ohye.

MR. OHYE: On the subject of quality of life, trying to get significant data from the study is the holy grail. I've been in this business about 40 years and here is a company that used a validated instrument.

I think it is accepted that .5 difference is not minimally significant. It is the number that you want to hit to show that you have achieved adequate quality of life. At least that's my impression here. Maybe I'm missing a point.

One last point, a general point with

reference to this first question, I think when you look at all of the data it is unusual to see when you have a myriad of studies like this that there are no outliers where you have one or two data points, primary or secondary, that go in the other direction. All of the data appear to me to go in the direction of this product is useful and safety.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: Just I guess an issue to bring up for discussion. I think the evidence of meaningful efficacy is I'm a little concerned with the proposed indication which says maintenance therapy. Admittedly, it doesn't say long-term maintenance therapy but what is the level of time that maintenance therapy includes from an FDA standpoint?

Is that a six-month study, a one-year study, a three-year study, a five-year study? Maintenance therapy potentially implies long-term usage of the drug although there clearly was no minimal long-term data presented.

MR. MARKS: I would note first that the

indication that you've seen is the indication as worded as requested by Genentech. That indication has not been any negotiated conclusion between the agency and Genentech. It is simply the indication requested by Genentech.

As regards the intended use, I believe the intended use is in essence very long-term use. Consequently some of the questions we are asking later on touch upon some aspects of that intention.

Lastly, with regards to the idea of how long they studied this one need to have before one can contemplate the long-term use of a product, I think that is very much dependent from a disease setting to disease setting. There are no agency standards for all diseases where a treatment is intended for long-term use. That is how long the efficacy has to be evaluated for.

Whether or not there has been sufficient evaluation -- I should say whether or not all of you feel there has been sufficient evaluation to contemplate that kind of use would be an important comment for us to be hearing.

CHAIRMAN PARSONS: Mr. Ohye.

MR. OHYE: On the subject of long-term use or chronic use drugs, I believe the FDA does have general guidelines with reference to the numbers of patients, the duration of therapy, the type of studies that were required.

As a matter of fact, if I were sitting on the research board of Genentech when they brought this program to me for review, I would compare the overall program that they have in mind against these general guidelines and what I am aware of happened in the case of other drugs that were approved for chronic therapy. I think the data presented today are well within the parameters of those general guidelines.

MR. MARKS: We have general guidelines on the safety testing for chronic disorders but, as I said, I think that for efficacy sorts of testing the nature of the disease very much directs what may be appropriate in each individual setting.

DR. WEISS: And the guidelines which you are probably referring to are the ICH guidelines for

chronic use for therapies for chronic use for diseases that are not serious or life threatening and are intended for chronic use are basically minimal criteria, the idea being that there are signals or extra areas of concern that you would want to go above even those minimum.

CHAIRMAN PARSONS: I think we'll move on to the second question which starts to get into some of the specifics that people have already started to talk about. I think this will encourage discussion.

The second question is:

2) Subjects receiving several types of chronic medications used in asthma management were excluded from the majority of the studies. Therefore, there are little to no efficacy data in such patients. For example, Studies 008 and 009 excluded patients receiving any of the following: leukotriene modifying agents, long-acting beta agonists, cromolyns, anticholinergies, oral steroids and xanthines.

Study 011 allowed long-acting beta agonists and oral steroids, but excluded the other

agents. Patients enrolled in Study 011 on average were on higher dosages of inhaled steroids than those in Studies 008 and 009.

In studies 008 and 009 significant differences were observed between treatment and placebo groups in the number of asthma exacerbations. However, Study 011 results were at best only partially suggestive of reductions of exacerbations associated with omalizumab use and only in patients on inhaled steroids. Among patients on oral steroids at enrollment there was no difference observed between treatment arms in exacerbations.

Of note, non-Caucasian patients were somewhat underrepresented compared to the prevalence in the general U.S. asthma population. No clear efficacy differences related to race were identified within the limited data available.

There are two parts to this question.

a) If approved, should the indicated population be limited to only the populations studied and in which efficacy has been shown, or is

it reasonable to extrapolate efficacy to wider populations? Populations to consider include:

- Patients receiving only inhaled steroids
- Patients receiving inhaled steroids irrespective of any other concomitant asthma controller medications
- Patients receiving maintenance therapy with oral steroids
- Any other allergic asthma subpopulations

Part B of the question is:

b) Should any of these populations be studied in additional controlled trials?

Also implied, I believe, in this question are there patient populations who should not receive the drug based on the information we've received at this time.

I'm going to open this up for discussion.

Dr. Fink.

DR. FINK: Well, ticking off one of the first parts, the use of other drugs. It's not normally a standard that says your drug has to be showing -- has to show efficacy compared to multiple

other controller agents. It clearly shows an added benefit to inhaled corticosteroids.

By its mechanism of action, it is unlikely that any of the other drugs would interfere with the effects seen with the study drug but it's probably a two-way street and may be more complex.

If you take IgE out of the allergic cascade, it may be that some of these other ancillary agents would lose much of their efficacy as additional add-on agents in the treatment of asthma once you took the allergic component out of asthma.

So I think it's a two-way street and you could equally well ask who has to meet the standard of treatment or do the studies. Does a leukotriene modifying become unnecessary if you are on omalizumab.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: I guess a couple of points in response to that. No. 1, I think it's important that it's not just that they are getting it but they are uncontrolled on inhaled steroids. I think that

is an important piece.

Secondly, experience would suggest that patients who are truly steroid dependent it's very hard to find anything to work, although we have heard some testimonial that it sometimes can. Clearly there is no data presented to us here to suggest that in that group as a whole it works. I would be uncomfortable with that.

Although I agree that I think to expect lots of comparative trials, which is what as clinicians we'd always like to see to know where a drug fits, but I don't think that is necessarily reasonable, in answer to Part B I would love to see a study that compares inhaled steroids plus Xolair to inhaled steroids plus a long-acting beta-agonist.

CHAIRMAN PARSONS: One question that I had as I looked through and maybe other committee members can help me is how do you decide who is controlled on inhaled steroids and who is not? Are there criteria out there that we can come up with that sort of state who actually is controlled?

I mean, there were no maximal doses used.

People didn't get pushed to maximal doses of inhaled steroids. There was made a determination that they were or were not controlled. Anybody have any comments on that?

Dr. Apter.

DR. APTER: Well, first of all, the NHLBI guidelines can be used to specify current control. For example, not needing short-acting beta-agonist more than twice a week. Not waking up at night. Improvement in peak flows. Also for research there's asthma control questionnaires. There are validated questionnaires.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: And related to this I think another way of assessing control and who really was studied and benefitted in this population, one could include that it would be patients not controlled on inhaled steroids and with an FEV1 on inhaled steroids less than 80 percent of predicted.

CHAIRMAN PARSONS: I think that is going to be fairly important for people who are prescribed this drug that they really have a clear

understanding of what not controlled on inhaled steroids means and what the other options are.

One of the other groups that -- a couple of the other comments that some people have expressed concerns about the elderly population. Are there concerns about ethnic minorities in terms of do they need to be studied more?

Dr. Chinchilli.

DR. CHINCHILLI: Yeah, I would recommend that studies be done in the minority populations. Did I hear right this morning that Genentech is going to collaborate with the intercity asthma study group on a study?

DR. JOHNSON: Charles Johnson, Genentech. Yes, we will be having discussions with the intercity working group. Dr. Busse, Dr. Morgan are representatives of that group and we are actually planning a meeting on Sunday evening to talk about possibilities for studying, mostly in those groups, children in the intercity asthma group.

DR. WEISS: Can I follow-up and ask if you have any thoughts, though? In addition to just

studies, what your thoughts would be in terms of study design. Do you think that should be placebo controlled trials or some type of direct comparison to other existing therapies?

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: I think the current standard of therapy really is combined with long-acting beta-agonists and inhaled steroids are certainly the most recent. The NIH guidelines suggest that. I think that one would never go wrong in a study by trying to see what this adds to this therapy.

CHAIRMAN PARSONS: Do people have comments regarding the population and should this drug become available? What about people are on maintenance therapy with oral steroids? What's the committee's feeling about that population in terms of efficacy shown and is that one that needs further study? Is this one that should be considered? That is part of this question.

Ms. Schell.

MS. SCHELL: I really believe that more people should be studied with oral steroids because,

again, I feel that our more severe asthmatics are treated with it as compared to inhaled. The ones that are on inhaled they go on bursts of the oral steroids a lot and those are the ones I'm concerned about.

Also, I have another question, if I may, regarding seasonal allergies. I guess it wasn't clear to me do you take this drug only during that season or do you take a maintenance dose all year long, or is this -- I wasn't clear on that part of it.

MR. MARKS: This product is intended as continuous treatment throughout.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: It's also, as far as I understand, not investigated for seasonable allergy so I don't know its efficacy at all.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: The seasonal allergy raises, particularly in pediatrics, an interesting question because there are many children who only have significant exacerbations in the spring or fall and

whether they need year-round treatment with a drug that is both injectable and expensive clearly should be investigated because maybe they only need it from February through June when it's the spring pollen season.

CHAIRMAN PARSONS: Do you think that starts to get into question No. 3, which we haven't left No. 2 yet, but specifically what the definition of allergic asthma is?

DR. FINK: If it doesn't, it's separate. The other comment I would like to make on oral steroids, I think it is important somehow in the labeling at least to indicate that patients on chronic oral steroids did not show benefit.

I think the wording has to be very careful there because many people are going to become confused about pulse steroids which did not seem to interrupt or show a problem with efficacy versus daily or every other day oral steroid therapy where it did not show a reduction in exacerbations.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: Regarding the proposed

indication, I would like it to say, "Inadequately controlled despite institution of the national guidelines." Although I don't feel like they compared it with the national guidelines, that would restrict the use even more than it would be otherwise to ones that really fail what we all think is national, what we should be doing for care.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: The only problem, I guess, I have with that concept, particularly when you get into adolescent intercity asthma which has some of the highest hospitalization and death rates for asthmatics, these are notoriously nonadherent patients.

The idea of saying that you are going to claim that they are taking three or four drugs regularly before you consider an injectable that you can control in your office doesn't necessarily make a lot of sense to me.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: The guidelines would only say that for control of medications you need two and the

two are now one. It's not that hard.

DR. FINK: Well, but then do you require that before a patient qualifies for this drug the parent has to stop smoking in the home?

DR. JOAD: No. I think -- what I'm saying is I don't think we need to do this study that you are saying to compare it with the best therapy that we now have because I think that would be a big expense.

I'm not sure it's really indicated to do that. I just think it shouldn't be added on until they have done their best according to the guidelines, which I think are extremely reasonable for intercity populations which I also take care of.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: This drug will be a big expense so I think it's very important to understand how it compares to the national recommended treatment. Of course, I do think it is very important to sort it out in the intercity population because they are at highest risk for a poor outcome.

CHAIRMAN PARSONS: I'm going to go on to

Dr. Schatz but just as a reminder that the discussion of cost is not part of what we have been asked to do today.

DR. SCHATZ: I just wanted to add one other perspective. We talk about intermittent exposure to remind us that intermittent -- again, anaphylaxis was not a big problem but one way to increase the incidence of anaphylaxis, at least to other agents, is to have intermittent exposure. I think that as we think about that as an option, I think we have to be concerned about that as an increased risk.

CHAIRMAN PARSONS: Following-up along with that, I had two questions. One is is there a patient population out there that we think is potentially at increased risk for anaphylaxis that we would recommend potentially not getting this drug in terms of answer to this question. Do people have thoughts about that?

The other population that came up in discussions earlier were people who had known malignancies and there have been some discussion

about whether those patients should be considered for this drug. Do people have comments on either of those?

Dr. Apter.

DR. APTER: I'm not concerned about anaphylaxis from the data shown because there were so few cases. I am concerned about the long term use of this medication and the use of the medication that can potentially modify the immune system in patients who have already had a diagnosis of cancer and would recommend against it.

Then cost. I realize we're not supposed to talk about cost but shifting the cost can shift which patients are affected. For example, when antihistamines went over the counter the cost shifted and certain patients could not get the medication. That eventually does affect the efficacy and the safety for patients. I find it's very hard to separate cost from safety and efficacy.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: Again, I would just like or the record point out that I understand why we don't

deal with cost, but I would submit that as a society I'm not so sure we really with limited resources have the -- whatever the right word is -- can no longer legitimately ignore that in terms of not dealing with cost effectiveness as an issue.

I would submit for the future that luxury to forget about cost that we seem to have to have here, I think, is not really warranted by the current world.

CHAIRMAN PARSONS: I'll let the FDA respond to that.

MR. MARKS: At the present time decisions regarding approval for marketing do not take into effect cost. While that is certainly a real world issue, there are other venues where that gets considered.

I realize you're not done here with this question, but before you leave it, two things. One is on the question you raised of patients with a prior history of malignancy or not, I think it might be more useful for us if you deferred that question until the later question which we are asking about

malignancies in broader terms and make that discussion comprehensive.

The second is before you leave this question about populations to extrapolate or not extrapolate, the issue of patients who are smoking was brought up for discussion earlier. I think before you leave this question we would like to hear some more opinions about whether or not that is a group of patients for whom extrapolate, generalization can be made or not.

CHAIRMAN PARSONS: Can we just complete the anaphylaxis group? Are there any concerns regarding anaphylaxis because those have come up before? Then why don't we move on to the smoking issue.

Dr. Swenson, you had a question.

DR. SWENSON: Well, I think that is an important question but I think it gets as sticky as this issue about not having studied patients on other controlling medications. In one case this is clearly something that is negative as opposed to other agents that would likely act favorably for

patients.

I almost put it in the same category that we may be -- is it right for us to advocate restricting it to nonsmokers but yet not asking that this drug be restricted to those people who seem not to improve with all other forms of standard present practice.

CHAIRMAN PARSONS: Maybe one way we could look at the question is do we feel that the data presented would indicate that we would expect the same efficacy in smokers. Or is there enough data to say that it is easily applicable to smokers or is there something specific about smokers to make us think this wouldn't work? Is that a way to look at it?

Dr. Schatz.

DR. SCHATZ: I would certainly like to see more data in smokers, but I think at this point to restrict it to nonsmokers would not be fair because as opposed to the nonallergic population, I think there is less.

There may be some but I think there is

less definite reason to say it's not going to work in smokers. I would like to see more data for sure in those patients specifically but I would not be in favor of restricting it to nonsmokers as I would allergic patients.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: A concern I guess I have, I'm not sure what to say about smokers. I think it needs to be studied there. By mechanism of action there is no obvious reason why it may not work in smokers.

What I think we will face as clinician is that the package insert and its wording is going to be critical to how the drug is used. We are in an era of managed care and managed care companies typically look at the minutiae of the package insert wording to decide what they have to cover and not provide coverage for.

I think how the package insert is worded is actually going to have a bigger effect potentially on how an expensive drug gets utilized or what managed care says is acceptable or

unacceptable use.

That makes the wording of the package insert really critical and I don't think it should err on the side of promoting or not promoting. I think it should probably say there is no data available on smoking asthmatics.

CHAIRMAN PARSONS: Dr. Atkinson.

DR. ATKINSON: I'd like to also -- that also brings up the sort of disappointing data on the oral steroid use which also those are the patients we are all the most concerned about. Many of the testimonials that we heard today were from people who were steroid dependent.

Those are the patients who are at risk for the greatest side effects, and yet the lack of efficacy that was shown in trials is going to be an incentive for providers not to provide coverage for any patient who is exactly in the category that we are most concerned about.

Something in the package wording and the wording of the package insert might be helpful, too, because, again, the variability in the patient

population we are seeing this with the beta-2 agonist receptor polymorphisms that have been shown now to produce big differences and responses to long-acting beta-agonists.

There may be a lot of variability in a population and people who are on chronic steroids may respond very, very well to this medicine and others may not.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: With regard to the smoking indication, I think it's important to bring in the cancer concerns here because that's a group that's at higher risk for getting cancer.

Since they didn't study people who were smoking and we are going to have to somehow deal with this concern about cancer, probably that's not a group who should be listed as being indicated for at this time.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: I don't recall if it was presented this morning. I can't recall it. In the patients who were taking all steroids, the

exacerbation rate was not less but what percent of patients who were on oral steroids who when they went on drug had a 50 percent reduction in their need for oral steroid?

That may be a key question. If there is a significant population that reduced their dose by at least half, that is significant even if exacerbation rates didn't fall.

CHAIRMAN PARSONS: Mr. Ohye.

MR. OHYE: I would like to suggest that with reference to oral steroids, it's not that the data weren't there. It's just that there were not enough numbers to have robust data.

CHAIRMAN PARSONS: So would you recommend increasing those numbers with addition studies? Would you recommend doing additional studies to increase those numbers?

MR. OHYE: I think that Genentech and Novartis will be a responsible company. I've competed against them so I can speak from my own personal experience. They are probably going to have a robust Phase IV program because that's the

responsible thing to do in this very, very difficult disease.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I just have one comment. I believe that the studies did include former smokers so there is -- I mean, in a sense former smokers' cancer risk does not decline to zero so there is that that can be stated, that there were former smokers who received this drug.

CHAIRMAN PARSONS: If there are not additional comments, I think we can move onto question 3. Do you need additional information regarding 2?

DR. WEISS: I was just wondering then if one could just sort of summarize that there are populations -- we're not really talking about indications and restricting or limiting indications but in terms of populations where you would like to see further studies, what always happens when we talk about approving some product is that there is a big effort to ask companies to study products further in Phase IV type studies.

There's greater attention to ensuring those Phase IV type studies are met over time.

What I seem to be hearing is that there is an interest in obtaining more information in certain groups of patients including perhaps smokers, people on other controller medications, perhaps elderly, perhaps other minority populations.

This is kind of the information that would be useful to us as we discuss with the sponsor, if we are coming towards a marketing approval, what kinds of additional studies to do in a post-marketing type of setting.

CHAIRMAN PARSONS: I think -- people, chime in. I think you have actually basically stated the ones that we came up with, the elderly population, smokers, patients on chronic steroids, and minorities.

Then again, patients who are actually on asthma medications per guidelines in terms of what is the additional benefit of this drug. Did I misstate that or do people have additional comments? I'm getting yeses. I'm not sure.

Dr. Fink.

DR. FINK: I guess I would just say in terms of optimal therapy according to NAEPP guidelines, if you have a patient on multiple controllers and they are not having exacerbations, I don't think many physicians would consider adding an additional therapy, particularly one that was injectable and costly.

I don't think the issue of can some of these patients be better controlled on multiple controllers is a big one in that if they are well controlled on multiple controllers, I don't think there would be many physicians going to this drug.

CHAIRMAN PARSONS: Dr. Atkinson.

DR. ATKINSON: I would like to add I guess there are ongoing studies but studies in children six to 12 which I think for allergic asthma is where a lot of the expense, if not the mortality, in asthma occurs.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: Also 12 to 17. The indications asked for 12 and I think that age group

like the elderly doesn't have much representation.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I would just like to make a plea that if this drug does go forward that in young individuals in particular that they should be followed long-term.

I also have a question that maybe somebody can answer. We've talked about the elderly but I wonder since IgE levels decrease with increasing age could it be that they were disproportionately excluded from the trial so it may be difficult to ever find enough numbers to do a specific study on the elderly.

CHAIRMAN PARSONS: Dr. Morris.

DR. MORRIS: I had a similar comment in that design of the following of patients of the older age group. If this is a continuous therapy and you get started at a certain age and you go on, part of the building-in of who to collect on are those particular people as a big surveillance project to know we're not going to necessarily be retesting their IgE when they are on therapy for

years and years and years at a time.

But surveillance data, cancer data particularly for those groups over a long period of time is exactly what we need because we are basing this on two pivotal studies that were relatively short compared to what the duration of therapy is now proposed. In the Phase IV and moving onward, the surveillance is critical for this type of administration.

CHAIRMAN PARSONS: And potentially particularly important to determine if the efficacy is maintained since we don't have enough data long-term to know what the efficacy looks like two years out.

Dr. Schatz.

DR. SCHATZ: Actually relevant to the issue of what proportion of elderly patients have positive skin tests, there are actually two recent studies. Not huge but one from Harlem Hospital and one from Baltimore, both of which suggest that either looking in vitro or by skin test more than 50 percent have positive reactions of elderly patients,

that is, over age 65 to indoor allergens. I think those patients are there to study.

CHAIRMAN PARSONS: And Dr. Apter.

DR. APTER: However, the significance of those positive tests clinically is not known. One old allergy caveat is you retain skin tests even after successful treatment with immunotherapy.

DR. SCHATZ: I mean, there is no question, of course, that you and I agree on that. I think that it is undoubtedly true that we would want any evidence of positive skin test to have a clinical correlation but I don't know how you are going to mandate that or even easily define it.

I happen to think from a practical standpoint at least showing it is going to be the best one can do but I certainly don't disagree that the next step, which is to try to understand its clinical importance. The difficulty of course with perennial allergens is it is very difficult to do.

DR. APTER: We are selecting patients based on skin tests so I think it gets to be problematic with the older patients, especially with

perennial allergens.

CHAIRMAN PARSONS: I think this goes into the discussion for question No. 3 so one more comment from Ms. Schell on No. 2 and then we'll move on.

MS. SCHELL: Yes. I was just wondering Dr. Fink's remarks about long-term controller medicine and maybe not looking at the study. When I look at patients' compliance and ease of taking medication, I would like to see a comparison. If they could cone off the long-term controllers and just be on the one shot a week, a month, or whatever, it would be more compliant for the patients.

I think it is significant to test that against somebody that may be on the full regime of the drug for them to take every day to go to one time to decrease the use of long-term controllers. maybe that is something we need to look at.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: The other area I think that ideally should be looked at in Phase IV studies is

what is an appropriate time interval for a trial off drug. I mean, if I've got a patient on inhaled corticosteroids who has gone a year with no hospitalizations, no ER visits, and minimal use of beta-2 agents, I would sure start tapering their dose aggressively.

I don't think it belongs in the package insert but I would sure like to know what is a reasonable prudent time interval. Is it 24 months of therapy or 36 months? Clearly with this drug you would have to take a patient off therapy to see if they still require continuation but I have no idea what is an appropriate time interval there.

CHAIRMAN PARSONS: I'm going to move on to question 3 because they keep getting harder. We'll need a little for these, I think.

If marketed, omalizumab would be the first passive immunotherapy for allergic asthma. documentation of atopy (e.g., skin reactivity) is frequently required prior to active immunotherapy. In the major efficacy trials, eligible patients had to have demonstrable skin reactivity to certain

aeroallergens as a defining criterion of allergic asthma.

a) Is it typical to classify patients as "allergic asthma" or "non-allergic asthma" in the current common practice of pulmonary/allergy medicine?

b) Does classifying a patient as having "allergic asthma" require a demonstration of skin reactivity? If not, what other criteria can be used?

c) If approved, should omalizumab be restricted to only patients who have documented skin test reactivity, or is it feasible to generalize findings to patients without an explicit reference to skin reactivity?

I'll open the discussion. I think the question here on the table is what is allergic asthma.

Dr. Joad.

DR. JOAD: I would strongly suggest to get on this drug they should have some test to prove allergy, skin test or in vitro test.

CHAIRMAN PARSONS: Dr. Morris.

DR. MORRIS: I think based on the efficacy data we have to comment on today the structure of the trial was a good one but we have to keep in mind that it was the structure of that trial that we are talking about this efficacy.

I think having the recommendation of the agency we would recommend the skin testing as something that would characterize the patients who would be deemed to have efficacy when on this drug.

That's not to mean that in the future there can't be further studies to say when it's opened up in criteria and then they come back and change and open up for the other groups of patients with asthma. For this indication I think limiting it to the skin testing.

CHAIRMAN PARSONS: Mr. Ohye.

MR. OHYE: I would ask the committee to consider whether you want to make this a condition preceded -- in other words, mandatory or something that you would highly recommend because that way you are really not getting into what happens in

everyone's office in the practice of medicine but you can highly recommend something based on what you see in the data.

CHAIRMAN PARSONS: We'll go down the row. Dr. Swenson.

DR. SWENSON: What about the issue of someone that might truly classically have a strong story for allergic asthma but the panel of antigens simply doesn't bear out to support that, i.e., that you're missing a certain antigen that that particular patient is very sensitive to?

I don't know whether we exclude people in whom if the history is strong enough clinically we would proceed with all the other recommendations about avoidance, etc. I don't know about how we deal with that question of a negative skin test or negative lab test.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: Again, I think Dr. Stoloff fairly eloquently presented the case for demonstrating specific IgE. The history may certainly be very suggestive but if you can't show

specific IgE to something, then a drug that works through that I don't think you can have confidence in.

I mean, I think we have to go with what we've got which is patients who were studied who had specific IgE and I don't see how we can do anything more than recommend and really, I think, in this case require until additional data suggest otherwise that these are the only patients who should receive it.

DR. SWENSON: Let me ask the definition of specific IgE. What if the patient has a strong history and has a high IgE level?

DR. SCHATZ: Again, that is not specific IgE as I think most allergist would consider it. Again, the data that we have before us don't us to say that group will benefit. Of course, there are other reasons for polyclonal increases than IgE that don't seem to be specific and the significance of that is not known. At least that would be my view.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: I think it's a nice concept and

I think it should be encouraged but I find how to write guidelines for it really bothersome. Are we talking about prick testing, intradermal testing, high-level intradermal testing, rash testing, how many antigens.

Is it allergic asthma if you have specific IgE against milk which generally has not been associated with significant wheezing. I mean, it raises a whole series of practical questions, unless you are going to limit and say it has to be a common air allergen. I think actually in this study it wasn't just sensitivity to an allergen. It was actually a common air allergen was their panel.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: Yes. I think it was to a perennial inhaled allergen to which there was exposure and that is how I would say it. I don't think it would be that difficult. I would include in vitro tests, valid in vitro tests, and whether it should be prick or appropriate delusion intradermal.

I think you might write it that appropriate skin testing and in vitro testing to a

perennial allergen to which the patient has exposure would be, I think, doable and I think would fit.

CHAIRMAN PARSONS: My concern would be that we already have less efficacy than we would like to see for the magic bullet obviously. If we expanded it to a patient population where there was no testing done, there are potentially a lot of patients who you would not expect to be able to respond to the medication and, therefore, the actual efficacy out in the general population would be even lower than what we've seen.

Dr. Apter, you had a comment?

DR. APTER: I would just agree with Dr. Schatz' definition. Skin testing is becoming more and more standardized so I think it will be easy to employ.

CHAIRMAN PARSONS: Are there specific issues with skin testing in the elderly that we need to look at additional tests in them? I'm asking this naively. Dr. Apter.

DR. APTER: Again, I think there is very little research on skin tests in the elderly. My

clinical experience is that many older individuals have positive tests to mites but I can't get a specific history of exposure to might-causing symptoms. The whole issue of this drug in the elderly becomes -- I think needs more study.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: A couple of issues. In one of the studies I quoted there was a significant pulmonary function difference in those who had the positive cockroach in this case, antibody versus not. It suggest that may it is significant, although I don't disagree with you.

Relative to skin testing in the elderly another issue is beta blockers. A lot of people are uncomfortable skin testing patients on beta blockers. That would be an additional -- I mean, this is a group that needs to be studied but it would be a reason why in vitro tests could be an alternative.

CHAIRMAN PARSONS: Are there additional comments regarding question No. 3 in terms of what appropriate allergy testing could be done to "define

allergic asthma and define the population?" It appears in general the group does agree that testing should be suggested, indicated prior to the institution of this medication based on the current data we have. Does that satisfy you?

That was an easier question than I thought so we'll move on to question No. 4 which is:

4) Substantial fractions of patients screened for these studies were ineligible for enrollment due to a baseline IgE concentrations that were outside the permitted limits (either too high or too low) or the IgE/weight combination gave an omalizumab dose greater than the maximum permitted of 750 mg q 4 weeks. This was especially true for the two open label studies.

Patients excluded from the study due to their IgE concentrations were not retested. However, in clinical practice, any patient whose IgE concentration does not fall within a permitted dosing range could be retested until a serum IgE concentration is in an acceptable dosing range.

a) Would this be appropriate? Please

address the stability or variability of IgE concentrations over time for an individual patient.

b) Can the clinical study findings be generalized to patients whose initial serum IgE concentrations preclude use of omalizumab therapy but where repetitive testing ultimately results in the detection of an acceptable serum concentration?

I would probably add in a c) here just to help which is:

c) Do we think that IgE concentrations should be measured in patients? There has already been some discussion about that because these questions in part imply that.

I'll open that up. I do recall in terms of question A that we did ask that question to Genentech specifically if they had data regarding variability of IgE levels over time in individual patients and they indicated that in some of the study patients they had done serial measurements of IgE levels and those were stable is what I recall.

MR. MARKS: Dr. Parsons, my recollection is that was over a two-week period approximately so

our question really may pertain to longer periods between retesting as well.

CHAIRMAN PARSONS: Okay.

Dr. Atkinson.

DR. ATKINSON: Yeah. First, I don't know about overall total IgE levels. It's well known, of course that specific IgE levels, which a lot of the discussion is arranged around, vary considerably depending on the season of the year and particular exacerbations.

The other issue is in childhood frequently asthma presents an early childhood and they continue on into adolescence or even longer and the natural history of IgE production is that it's going to increase over time. You may test a two-year-old who might not qualify but at age 4 they might. To my mind clearly the answer is yes and that they should be. Serial testing is not something that should be a problem.

CHAIRMAN PARSONS: We'll go to Dr. Schatz and then Dr. Fink.

DR. SCHATZ: I recall hearing data that I

thought was longer term presented that in adults there was not much variability in serum IgE so the concept, I think this question may not come up very often in the sense that it doesn't change enough to worry about.

I think we have to measure serum IgE not because most of us do it clinically but obviously if we're going to think about using it, we have to do that for dosage so I think the only reason to measure it is to make sure they fit within the dosing criteria.

My understanding of what I heard in terms of population data was that in adults, at least, and in the age group, I think, at least most of the age group that this is being recommended, it doesn't change significantly. We wouldn't expect this to be a significant issue.

CHAIRMAN PARSONS: Can we ask them for specific clarification if the company does have specific longer term data?

MR. MARKS: Yes, please do. Also I would ask that you consider whether the population data is

getting at the question. If there is substantial variability the population may be stable but if there is substantial individual variability, it means that an individual might rise into or might fall into a permitted dosing range but yet much of the time be out of it and, therefore, that's part of our concern.

CHAIRMAN PARSONS: And that's the data from the Arizona group which the patient populations over time is mean data is my understanding. My question to the company which they said they had data for was on individual patients what is the relative stability over time.

DR. JOHNSON: I'm afraid that all of the data that we have to show is actually plotted as means for the population. We haven't examined the individual variability over a period of time but we did collect IgE values in the placebo groups over that 52-week period. We can certainly go back and revisit in terms of the individual patient variability across that time.

CHAIRMAN PARSONS: I think that would

potentially be helpful to answer the question because the question is if you do a single test and it's "negative," you need to do a repeat. The other question that I would have in this regard goes back to how long do you stay on this drug question which is, indeed, if IgE levels are higher in children and they decrease as adults, how do you decide that they stay on for a long time. I realize we're supposed to be answering questions but I'm asking that one.

Dr. Fink.

DR. FINK: I think it raises two questions actually. One, and I didn't hear an exact answer to this, although maybe a little indication, if you use too much Xolair, does it increase risk of side effects because there was some indication, at least, in terms of anaphylaxis having higher levels of free Xolair might increase risk of rash and maybe anaphylaxis. Using too much drug may be a bad thing.

The other side of the coin is I'm not sure if we're asking the right question. Should we be asking the question of the stability of IgE levels

or with this drug should we be looking at the idea that you should actually check IgE levels on therapy and as long as you are achieving a level of 10 to 25 micrograms, you know you're in the right therapeutic range. Looking at suppression of free IgE as your therapeutic endpoint for titrating drug rather than necessarily initial IgE level.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I actually have a question. Can you be sure that symptoms correlate with IgE levels? If the patient is feeling better on the medication and the IgE level is unchanged, then what do you do?

CHAIRMAN PARSONS: I'm going to let Dr. Schatz answer that question.

DR. SCHATZ: I'm going to ask a question but I know reading in here there was a statement that measuring IgE levels on a person who is on the Xolair is problematic and maybe I could be reminded as to why.

MR. MARKS: While they are on Xolair the total IgE, most of which is bound to the product,

goes up because most of it is bound to omalizumab so you can't adjust your dosing by that because the initial dose determination is based on total IgE which is all the free IgE. The free IgE while you are on treatment becomes very much lower.

DR. SCHATZ: So I would extrapolate to that that you can't really use then serum IgE to follow the course of your patients in a patient who is on the drug.

MR. MARKS: Yes, that is correct. You can't use that.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: Is that correct or is that correct only right after dosing because the complex antibody is very rapidly cleared from the kidneys so if you check a free serum IgE level 72 hours, 96 hours after giving the drug, it should reflect unbound drug.

MR. MARKS: No. Actually, the ability to dose this only once every four weeks is due to the long persistence of the omalizumab within the patient.

DR. FINK: Right, but the data they presented they showed trough data in the 25 nanogram range.

MR. MARKS: That was the free IgE.

DR. FINK: Right. Wasn't that --

MR. MARKS: That was not the total IgE. The total IgE is very much higher is composed of the free IgE plus the IgE that is bound to the omalizumab.

DR. FINK: What do you get with standard laboratory measurements for your total?

CHAIRMAN PARSONS: My understanding, too, is two specific assays. You have to specifically measure and it's total that we get in the clinical lab. We are all nodding yes.

MR. MARKS: And it's based upon that total in the absence of omalizumab that the dosing parameters were developed.

CHAIRMAN PARSONS: Dr. Morris had a question or comment.

DR. MORRIS: It's more of a comment. The way of thinking about the IgE levels of initially

using that as a screen to make sure we're in the right patient population. But to bring up another series of data or way of looking at the data, on page 122 of the agency's handout, Table 102 looked at quartile responses or exacerbations based on quartile IgE baseline.

It didn't seem like there was a credation to the rate of exacerbation based on their baseline IgE. But it does maybe help us get the right target population initially to say we are in the ballpark but monitor it later on. I'm not too sure based on these data.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: This just looks like a simple question that the company could answer for us with very little investment of money in a study to just answer it for the physicians who want to use it. You know, how often should we retest if they don't qualify. How stable is it. It strikes me as a very easily ascertained data that the company could get. If you are looking for a study, that's not much of a study but it's important data.

CHAIRMAN PARSONS: Second part of the question actually is: Can the clinical study findings be generalized to patients whose initial serum IgE concentrations precluded the use of Xolair therapy but where repetitive testing ultimately results in the detection of an acceptable serum concentration since those patients with an initial negative test would have been excluded from the trial.

Do people have comments regarding that? If somebody's IgE level now changes over time, are they similar to the patients who are enrolled in the study or do they potentially represent a different population?

DR. JOAD: I can't imagine it really matters. I would think if they qualify, they qualify and we just follow it. I wouldn't try to figure that out.

CHAIRMAN PARSONS: Dr. Atkinson.

DR. ATKINSON: I sort of field that if someone's IgE actually was higher and they were in the category that's too high, if they are strongly

atopic and they've got asthma, that they probably would benefit from it, or they would stand a good chance of benefitting from this therapy. Even if they were higher than had been tested, I think given the rational reason for the efficacy of the medication they should benefit.

The other thing is that probably there is no data but you would expect sort of a stepwise reduction in that IgE over time as you are administering the product. The half-lives of these two immmunoglobulins are very different in the serum so you are producing a lot of IgE or the turnover rate is a lot faster for IgE than the product. I would expect that somebody whose IgE was higher than the limits that were tested would still benefit but would have to be tested.

MR. MARKS: Could you comment that if they were excluded from the dosing table, the dosing regime due to having too high an IgE and were subsequently tested and were found to fit within the known dosing parameters, would you be concerned that their normal IgE level might -- normal indulgence

production might be actually at that higher level such that with the dose of omalizumab that they receive based upon that one time lower dose they might, in fact, be under dosed as compared to their usual circumstance.

DR. ATKINSON: I don't think you could estimate what -- you could estimate what dose and whatever rationale that company has been using for estimating what doses would be necessary. I think there is a concern about toxicity of going too high on the medication but over time you should be able to lower the IgE level. I don't know whether they have any data on very high levels, whether that was ever tested or not.

MR. MARKS: We don't have any extensive data on that because that was to be excluded due to the limitations on how much product can be administered.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: Again, I think the data that will be looked at has been presented as a population but looked at as individuals will help us know what

proportion of patients really have such fluctuating IgE.

I think the question of if they really were a population, say two populations, one that was very stable looking like the mean and another that bounced up and down, one could wonder whether that bouncy IgE population truly is similar to the current population and, as I say, whether that population exist I think could be looked at from these individual data.

In the meantime I really agree that if they end up qualifying I wouldn't necessarily put anything in here or believe that we shouldn't go ahead and have that patient be treated as if they qualify the first time.

CHAIRMAN PARSONS: If there is no further discussion, we'll move on to Question 5. Did you have additional issues?

I think we have, in part, answered question 5. I'll read it so it's part of the record and for additional discussion.

5) Fluctuation in IgE within a patient

over long periods of time may potentially impact efficacy. Dosing is based upon weight and pre-treatment IgE concentration. IgE levels cannot be re-evaluated while receiving omalizumab, or for an extended period after dosing is discontinued, because the omalizumab alters the apparent serum IgE concentration. In the clinical studies, the effect of omalizumab on asthma exacerbations appeared to persist through 1 year of dosing.

A patient whose intrinsic IgE levels rise substantially during treatment will receive a dose lower than recommended. Since IgE is not retested, it will not be known if the dose requires adjustment.

Are IgE levels in individual allergic asthma patients stable over long periods of time (e.g., years)? Is it reasonable to base long-term treatment and the expectation of sustained efficacy on a one-time evaluation of IgE concentration?

I think we have addressed this question. Are there additional discussion or points for this? Additional comments? Did you want anything more

than that? Do you have additional questions regarding this specific issue?

DR. WEISS: Maybe you can then reiterate if -- this is a question Dr. Fink brought up in a slightly different way about how long do you manage somebody who is controlled in terms of when do you stop medication. It is sort of a similar type of issue which is how long do you know that you should continue to treat people.

In this case you don't really have any marker to also go by. Is this product is intended for very, very long-term treatment, I think it will be helpful to have some thoughts from the committee. Maybe how best to evaluate that particular issue.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: Most guidelines talk about always trying to get to a lowest effective dose so I think the concept of building in some idea that at some point one would say taper or try to discontinue is certainly reasonable.

I don't think we have much information as to how to give those guidelines. But since most of

the data have gone up to a year, one could really just not on the basis of data but almost sort of a general practice sort of thing and the lowest effective dose concept would be to consider a trial discontinuation after a year.

There are lots of reasons to think that a substantial proportion may reexacerbate but there may certainly be a group who won't continue to need it. I don't think we have data to answer that question but I think the concept of trying to get to the lowest effective dose is built into all of our current guidelines and should be thought of in this context as well.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: It's a sort of correlated question which is if a patient on Xolair has an exacerbation are they a good candidate to continue the drug since we saw a fairly small proportion of patients did have exacerbations, or does the presence of continued exacerbations on Xolair say this is a patient who is a nonresponder and shouldn't continue the drug.

CHAIRMAN PARSONS: I think those are excellent questions. I mean, I think that based on our current practice with other medications, many patients would then be considered nonresponders and an alternate therapy would be chosen such that those who responded would be continued on.

DR. WEISS: Would that be a study design that would be useful to take people who have experience with exacerbations and randomize them to staying on medication or coming off as sort of a randomized withdrawal kind of design in a selected population?

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: I think it would. One difficulty, though, is you would have to individualize, I think, to some extent the reason for the exacerbations. We all have patients who are very well controlled but they get the wrong virus or whatever combination of events.

I think that is the difficulty. I certainly agree overall nonresponders shouldn't continue something but I think one would have to be

sure of the nonresponders and exacerbation that might have happened with the best of anything.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: Just randomization according to criteria should distribute those patients equally.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I'm just looking at the other side of the coin. What if you have a patient who does respond and you try to taper off and you do taper the drug off and then the patient has recurrent symptoms but you recheck an IgE level and it's too low to restart the drug. I just raise this as an issue of having absolute limits for starting the drug according to IgE level.

CHAIRMAN PARSONS: Part of that may be what we consider a responder as clinicians. There are people who "feel better" but if you actually do some of the specific studies, more of the objective tests, you often times don't see specific responses. That has been an issue with inhaled steroids, oral steroids, and others. This is a confounding issue

often for some of these medications.

DR. DORES: But my question is if the IgE level was high enough the first time around to receive the drug but the second time around it's not, is it fair to put the same limits on the IgE level?

CHAIRMAN PARSONS: I personally think since we don't really know what happens to IgE levels in an individual over time, it's hard to know. It's hard to answer that question. Other people have thoughts?

DR. APTER: That's where the trial that you suggested might help sort that out if people were randomized to restarting versus not.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: The discontinuation data on Xolair does show that most patients within six to eight weeks return to their baseline level so it would really only be an issue if you had the patient who was just borderline "qualified" and then had been 80 and fell to 65. Would you exclude them? I think you leave that up to the decision of the clinician

and the patient. Maybe the insurance company.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: I think, and you can correct me, a lot of the discontinuation data was still at least than a year and another way to study the discontinuation, which has been done with other therapy, would be after a year to randomly discontinue some and continue others. Keep track of their characteristics and I think that might help understand some issues.

CHAIRMAN PARSONS: In the essence of time, I know there are a couple of committee members that need to leave by 4:00 so if we can continue without a break. Can I get a vote for that? We're not supposed to be voting on anything else but if I could just get thumbs up from the committee to continue with the discussions. We seem to be doing okay. Is that all right? We are going to continue on then to make sure we have a quorum for the entire time.

We are going to move on to the next

question, No. 6.

6) Malignancies were an uncommon occurrence during clinical trials. However, of all malignancies observed, 20 occurred in approximately 3,000 patient-years with omalizumab, and 5 in approximately 1,500 patient-years in control groups (rates of 6.3/1000 patient-years compared to 3.3/1,000 patient-years).

There were a variety of cancer types in both groups. Non-melanoma skin cancers occurred with approximate equal frequency in both groups. The rate increase in cancers associated with omalizumab was approximately 3.7 per 1,000 patient-years for cancers other than non-melanoma skin cancer.

a) Please discuss the degree to which these data suggest that there is a risk of cancer associated with omalizumab treatment. If approved, what types of information or emphasis should be included in product labeling about malignancy?

b) How should the evaluation of any potential association with omalizumab and malignancy

be further evaluated?

I'll open it up. Dr. Dores.

DR. DORES: I would like to say that I don't think there is sufficient information one way or another to say that there is an increased risk or there is not an increased risk of malignancy.

I think the fact that 60 percent of the malignancies occurred within six months and 18 out of 20 within one year may sit highly unlikely that we can implicate one medication because knowing what we know about latency and cancer development, this is a process that takes years. I think if it's even under five years, it would be unusual but possible.

One caveat is could we potentially see different risks for lymphoproliferative disorders since Ige will be affecting the immune system. One thing that I have to really struggle with is just that the latency period is insufficient so people really need to be followed who receive this medication.

The other thing is that the definition of cancer, I think, including people who had recurrent

disease is confounding this. I think the data that Dr. Tarone presented comparing to the SEER data where he excluded recurrent disease and non-small cell skin cancer is something that we can use fairly comparably, although we know that all people in SEER do not have asthma.

Anyway, the numbers -- so I think you have to decide and to make the study cleaner that you are going to exclude people with any malignancy. I would favor excluding people with malignancy because it's just going to be very difficult to study.

The other thing that was pointed out, and I believe by Dr. Tarone as well, is that there is a detection by bias. People in the control group or in some studies seem less frequently than people who received the study drug.

When we look at all of the analyses compared to the control population there is no significant increased risk but you have to understand that you have small numbers. I would expect that you wouldn't see any significant increase in cancer risk because the numbers are just

too small. You don't have the power to detect that.

I think comparison with the SEER data in the literature we were provided a breakdown of male and female and there was an isolated significant increased risk in males, I believe.

But, again, I think you can only fairly do that comparison by excluding people who had recurrent disease because you should be comparing the same way that SEER reports data and that is only with the first cancer.

I think I'm done unless you have other specific questions.

DR. SCHATZ: I have a question for you actually. Would you make a prior history of cancer a contraindication to use of this medicine?

DR. DORES: Well, I think I would favor -- not knowing, and I guess that's where I feel most insecure is that we don't have data one way or another. Probably the group that I would allow in are non-small cell skin cancers.

CHAIRMAN PARSONS: Does anybody on the committee know if there are in any of the large

asthma databases or in the large cancer databases enough information regarding the patient's malignancy status in the asthma databases and atopic status in the cancer databases that we could sort of -- one of the questions that worries me is is IgE protective against cancer in a very gross manner.

That is coming from more of a critical care sepsis experience where there we were pretty convinced that tumor necrosis factor was not a good thing and using anti-TNF antibodies and some of those patients turned out not to always do well.

Things that look harmful often times have some potential benefits that we only discover later after we've determined that we thought they were all bad. Like everything in life, probably nothing really is truly all bad or all good.

Is there any way to get at the information of are people who are atopic somehow protected in some sense from malignancies? It sounds like the animal studies are going to be difficult. Are there data? Is the FDA interested in see that data?

DR. WEISS: We're always interested in

seeing data. It's just that we obviously haven't had a chance to evaluate it. I think this is new information that you -- no? Not new information. I think if time permits. I mean, if it's a quick summary we probably wouldn't mind seeing it.

CHAIRMAN PARSONS: We'll do a three-minute limit. How's that?

Dr. Dores.

DR. DORES: Just one quick thing while they are setting up. I think I said the wrong thing. The people that I would allow in the study are non-melanoma skin cancers. I'm sorry. I think I said non-small cell.

DR. WEISS: We knew what you meant.

DR. TARONE: Actually, the story with allergy, asthma, and the common story in epidemiology, there are some initial case control studies that show something very interesting. But then subsequent study in cohort studies and more recent studies tend not to support that.

This is the result of a medanalysis that was done by Dr. Patricia Tennis. This summarizes

cohort studies so these are where you identify asthma cohorts and then follow them through time and compare their cancer rates to either a control population or to some general population rates.

These studies, there's one study that sort of looks like an outlier. This is a Swedish study that showed a protective effect. Overall the studies were right around the relative risk of one. This was the only incidence.

There have also been two large cohort studies of mortality. Robinet and Fraumeni studied 9,000 military personnel with asthma. They reported a 30 percent increase in cancer mortality. Alderson studied 2,000 men and women with asthma and reported a 30 percent decrease in cancer mortality.

Actually there have been two studies published, cohort follow-up studies this year, 2003, one in the American Journal of Epidemiology based on an Australian cohort of 3,000 asthmatics. They reported cancer rates for the most common types of cancer.

This is complicated so because of the time

let's just look at it. You can see where there was one instance where they saw a protective effect in the asthma patients but in every other case, the risk was elevated significantly so for prostate cancer.

They also looked separately at patients with a positive skin test to different allergens. In fact, the risk tended to be a little more elevated. There was no evidence of a protective effect. Then a subsequent study -- yes, this is it. This is a French cohort study that was published in the European Respiratory Journal in 2003.

Again, they found a relative risk of death. This is death. The Australian study was incidence. They found a relative risk of 1.1. The studies overall show no protective effect of asthma or allergy for cancer risk.

CHAIRMAN PARSONS: I guess my comment at this point would be I would agree with the recommendation that anybody that has a known malignancy sort of a non-melanoma skin cancer probably shouldn't be included.

I would also be concerned because of the potential longevity or duration that some of these patients will be on this medication. If a child is started on it, they can be on it for years as can be adults.

My concern would be if there is any potential for increased cancer risk that monitoring is going to be critical. I would err on the side of excluding patients from getting the drug based on that risk if there was any potential increase in the population. cigarette smokers, I think, need to be looked at more carefully.

I think anybody with a known malignancy needs to come out. I think the other thing that maybe should be considered is a strong family history of a malignancy potentially should be considered as well. Do other committee members have comments?

Dr. Ohye. Mr. Ohye.

MR. OHYE: It's Mister. I'm just a, "Yeah, you" representing the dark side.

With reference to labeling I think you

have to consider whether if you're talking about an absolute contraindication or warning or precaution. I would suggest that you are operating in the area of warning or a precaution and not an absolute contraindication.

CHAIRMAN PARSONS:

MR. MARKS: I think we are very interested in hearing your level of concern but we are not actually asking the committee to determine exact phrasing of the labeling or exact positioning in the labeling.

While I do want to hear the other comments of people, one thing that I would ask for comments on is Dr. Dores and others have suggested that this warrants long-term follow-up information.

A question that I have in helping us to understand how to structure that is while we can certainly follow long-term patients on omalizumab, how are we going to form a conclusion from that information?

The SEER data is certainly available. We've seen in the data that we have in hand so far

that the concern about malignancies arises more from the comparison to the controlled group in the studies than from the comparison to the SEER data. So advice you can give us on how we should structure the longer term studies in order to help us in forming a valid conclusion. After all, the cohort studies suggest that HOV may not be protective. Nonetheless, we have the limited amount of data from one year here that suggest that there is a difference.

DR. SCHATZ: While controlled data, I'm sure, would be in some ways the best numbers that are going to be very important and I would wonder whether one should try to create a registry where at least voluntarily as many patients as possible who are treated with this post-marketing are actually registered and some attempt to follow.

The larger those numbers, the more than a comparison to the normative United States data I think would be useful. I'm not saying that would be the exclusive way to do it but I think it would provide additional help with the signal.

CHAIRMAN PARSONS: I think, though, that doesn't get at the issue of the control population potentially having a lower risk. That's a more complex question to get at. I guess the question is if there clearly have been the placebo group to date in trials, is it possible to follow them out or patients that are excluded from the drug or patients who choose not to take the drug.

I mean, is there a way to capture that patient population. It's a bigger question than just related to this drug. The big question is is there any protective effective IgE specifically in cancer.

DR. JOAD: I'm not an epidemiologist but I thought that's what case control studies did. You took a case and then you took two people who were similar to the case but didn't get the drug.

Somebody who is an epidemiologist tell me. I thought that's how you figure out whether something -- I can't imagine you can do it with a controlled trial. It's just too infrequent an event. You know that.

DR. DORES: Part of the problem is that people have not taken this medication for long enough. A case control study is not going to be meaningful without sufficient latency so at this point really you have to look forward.

DR. JOAD: That's what I meant. I mean, once it's released, can't there be the registry that Dr. Schatz wants and then they do case control study with all the cases. At some point along the way you will be able to figure out if there is an increased risk or not.

DR. DORES: Either way, I mean, it's going to take follow-up. I mean, it's going to take large numbers so case control may eventually be appropriate but still you are going to need to collect large numbers of patients simply because cancer is an infrequent endpoint.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: I think it's horribly complex because the fact that we are looking more likely for loss of a protective effect rather than a harmful effect means that your case control study to be

valid the case controls would have to have allergic asthma never exposed to the drug. That would be tremendously difficult to do as a case controlled study. Not impossible but tremendously difficult.

DR. JOAD: You must think everybody is going to get this drug once it's released.

DR. FINK: No. I am concerned -- I think my concern is this data is worrisome and it may depend on the population that gets the drug. If you are talking about patients with severe debilitating or life-threatening asthma, I think it would be pretty safe to say the risk benefit ratio is in their favor for receiving this drug if they are a good responder.

The more this drug potentially gets used in the market place as a replacement. As we heard some people say, it might be easier to take a shot once a month than to take an inhaled drug plus an oral drug, something like that. The more this drug gets widely used, the greater the danger that the risk benefit ratio may shift to an undesirable number becomes if there is an increased cancer risk

or loss of protection.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: I think the point you make about the loss of a protective effect being harder to identify is important. But I think the data we've just seen is reassuring in the sense that maybe there isn't as much of a protective effect as one might have thought from earlier studies.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I have a question for the FDA, though. You must run across this issue with several drugs as far as potential to cause cancer. When there is just not enough experience, how much evidence do you need? I mean, how do you evaluate that because I think all we can tell you is there is no data to say this causes or does not cause malignancy.

MR. MARKS: I think that, yes, this is a question that comes up at various stages in a drug's life. Some at this stage and some at later stages. At this stage, of course, the question is going to be how large a concern does one have and how

important is that concern. In this case we are talking about cancer.

The question will be how concerned is the committee that that is a real finding and then balancing that, of course, against the efficacy that was seen in determining whether or not one can recommend that there is a favorable or unfavorable risk benefit.

The other question is of the longer-term follow-up question. That particularly comes up in products where we develop a concern with cancer after it is marketed and it is often very hard to answer that question. That really was the heart of my question to you, what can you recommend to us in going about studying that?

What techniques or study methods do you think might be particularly useful that we can try to employ. You are shaking your head. I can see it's not an easy question and that is particularly why we are asking for advice.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I'm not sure I can give that

advice and having some experience in second cancers and treatment related effects is something that takes time. I'm not sure there is any easy way unless you start to see adverse effects early on.

DR. WEISS: One of the reasons this has come up now, of course, is that we do see this slight difference in control trials. You also have the comparisons, as we have discussed, with the SEER database and the limitations. With that advantages that would be helpful which apparently is not really available as well as we would like would be the history of databases in the particular population.

We have dealt with this to some extent in the rheumatology population with the advent of TNF-blocking therapies and concerns about a specific type of malignancy there, lymphoma, biological plausibility, and a number of products within the same class where you see some consistent imbalance.

We don't have a lot of products for the same class. This is the first one. It has raised an issue because there is this somewhat imbalance. As Dr. Walton said, trying to put this in

perspective is at this stage we realize is an extremely difficult question that we have wrestled with.

I guess it is somewhat gratifying that you all are wrestling with it as well. There are two very short questions. I know time is limited. One is you all talked some about whether to suggest contraindicating or warning or whatever people at risk. We would agree that something that is a contraindication would be potentially a problem.

One, because it would make it very difficult to study certain populations. Would it be feasible to try to enrich a population? For instance, we don't have much data on smokers.

If that is a population where there is -- maybe the rate of cancers would be expected to be higher anyway and to do a trial in a particular population that is sort of enriched for having -- you know, if we knew there was harm we wouldn't want that population studied but we don't have any information. Would that be a way to try to get an answer about any kind of loss of protective effect

in a reasonable time frame?

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I guess one main concern is that I am not sure you could extrapolate and say that smokers are going to reflect the rest of the population. It may be a finding for smoking and lung cancer but if there is some interaction with the drug, it doesn't mean that you're not -- that you will or will not see it in nonsmokers. I just don't think you can generalize. I also would have a concern about lymphoproliferative disorders.

DR. WEISS: Except that we didn't see a preponderance. I mean, if we saw a preponderance of lymphoproliferative disorders and lymphomas. We didn't see a preponderance of any one. We certainly didn't see a preponderance of lymphomas in the dataset that we have. Obviously it is something we would want to look at over time.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I just really caution about just thinking about the latency, that there just isn't enough time. I mean, potentially. I mean, a

lymphoma or other cancer could have developed within three months and, yes, we would be sitting here and things would be easy. We might not be sitting here. But it's just you have to be very careful that we just probably don't have enough time.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: The concern, although it didn't show up yet, of lymphoproliferative disorder raises a question in my mind as a pediatrician if you extend trials of this drug, particularly into the early adolescent age group and the younger child, the child between six and 12 where lymphoproliferative disorders are much more common than in adulthood, will we be exposing that population to undue risk. Now, it might unmask a signal but is that a wise thing to do?

CHAIRMAN PARSONS: Are there further comments regarding the level of concern of malignancy?

DR. WEISS: It was raised by some people in some side discussions about some imbalances with respect to the breast cancer numbers that saw. I

was just wondering if, especially Dr. Dores, you've had any comment on that or is does that raise anything in particular?

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: Again, I think you have to be very careful of some of the cases the patients had presented before entering the study. Again, the latency associated with breast cancer is years. It would be very, very unlikely that you would have malignant process in the breast develop over this short time frame.

I mean, I did go through each case and I'm not sure that I would -- in particular the lymphoma was a little concerning and extra data was presented today but, you know, I'm not sure that you can say anything about these cases simply because of the short time frame.

CHAIRMAN PARSONS: Dr. Atkinson.

DR. ATKINSON: I would like to just make one more comment that had to do with the discussion about the animal model earlier. There was one paper that was presented by the agency on a family that

was supposed to be IgE deficient but there hasn't been a single individual identified as far as I am aware whose got a genetic deficiency of IgE that could be maybe comparable to the effects of this medication.

But there are individuals with primary immunodeficiencies who are born without any ability to make IgE. The one that we encounter the most often is X-linked A gamma globulin anemia. Those patients may have a very slight increase in their rate of observed malignancies but it is even questionable.

Certainly during the many patients that we've followed over the last 10 or 20 years that I'm familiar with it at UAB, I don't recall ever seeing one in that patient category. It seems the simple absence of IgE does seem by itself to be a big risk factor. I'll let somebody who knows something.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I guess I would just say that we need to see the numbers for that. We would need to see the risk and the confidence intervals. Then

I would be swayed by that.

I guess one other thing that you might think about, or rethink, is just whether there is any potential for animal model, simply because this is such a long-term follow-up process for a human being that if there is anyway that you could have a mouse model, for example, that's prone to a specific cancer or lymphoproliferative disorder and see what happens when they are administered the drug and see what happens in an animal model that in any way might be helpful.

Although I realize there are limitations, but I'm just suggesting that it be revisited as a possibility.

CHAIRMAN PARSONS: Any additional comments? We'll move on to question No. 7.

7) In clinical trials, 3 anaphylaxis events occurred among omalizumab treated patients within 2 hours of treatment without obvious other triggers, compared with 1 anaphylaxis event without known trigger in the control patients. Other, lesser, allergic reactions were also observed in

omalizumab treated patients.

Please discuss the strength of the association between omalizumab and anaphylaxis, and the degree of concern regarding allergic reactions in this patient population. Do these findings necessitate any specific precautions for use of omalizumab?

I'll open it up to the committee.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: I guess one of the things that I wondered about was it was a late onset like they mentioned, 90 minutes to two hours. Does that mean -- I don't think it precludes the use of Xolair but does that mean they should go get their injections in the doctor's office and stay for two hours? To me it does say that.

CHAIRMAN PARSONS: I had a question. Because of the two that did occur at 90 minutes, is there something in the vehicle that is being used that is potentially allergic causing anaphylaxis in this patient population. Is there a vehicle issue because it was a relatively small number.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: Weren't both of the patients where that occurred early on IV exposure rather than subcutaneous?

CHAIRMAN PARSONS: I thought one was subcu and one was IV.

DR. FINK: One and one.

CHAIRMAN PARSONS: One and one.

DR. FINK: Oh, boy.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: I'm not sure. I'm not sure what to say about the waiting period but I think it would be hard to mandate that long a waiting period even though there is a concern about that. I think clearly the one think that should, and it probably would anyway, but in the insert say this has to be given in facilities and with personnel available to treat a systemic allergic reaction. That would be one answer to the question.

CHAIRMAN PARSONS: Dr. Atkinson.

DR. ATKINSON: If I recall correctly, one or both of those patients had had systemic reactions

before and had anaphylaxis before. Is that correct? I mean, that could be added as an additional caution to the practitioner that if the patient had had documented anaphylaxis previously or systemic reactions to immunotherapy they might be at increased risk. I believe I recall that one or more of those patients had had systemic anaphylaxis in previous examples.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: I guess I'm not real concerned about the anaphylaxis issue in that if you can extrapolate data from other human monoclonals that have been in clinical use, occurrence of anaphylactoid reactions has been extraordinarily rare.

I don't think there is any reason that having the binding site directly mediated against IgE should necessarily alter that. There is part of me that says anaphylaxis shouldn't really be brought up as a major issue in the labeling if we can trust data from other human monoclonals.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I guess I just have one question. Maybe because in oncology we use different monoclonals, but are they usually administered with a steroid or other agent that might decrease allergy whereas this one is not?

MR. MARKS: Certain other products are administered with pretreatment. As you note, this one is not.

CHAIRMAN PARSONS: I guess I share some of Dr. Joad's concerns in that although the rate of anaphylaxis was low, it was higher than in controls and if this actually -- how many millions of people are out there with asthma so even a low incidence of a potential adverse event actually can impact a large number of people.

I wonder if it's not worth at least going forward to monitor closely, consider close observation after they have been given the drug so they get more information on a larger patient population as the drug goes forward to see what the actual incidence is because it does appear to be higher than in controls.

Dr. Fink.

DR. FINK: Do you observe that with first dose or subsequent doses? I mean, it is a significant burden on caregivers if you say every dose has to be observed for 30, 60, 90 minutes based on probably in excess of one case.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: I have a little trouble with the mechanism for anaphylaxis. If you are mopping up all the IgE, the IgE won't help mast cells degranulate. Of course, in chemotherapy there are other mechanisms that cause anaphylactic-like reactions. I'm not sure but I think these patients should be observed. I don't want to keep them for an hour and a half.

CHAIRMAN PARSONS: Dr. Dores.

DR. DORES: I guess my point was more of a question because I've only given monoclonal antibodies with pretreatment but that is a different monoclonal antibody. The question was if the monoclonal antibodies you were referring to were often administered with antihistamines or steroids.

The other point is that some of these patients that will be receiving this drug will already be on systemic steroids.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: It's not exactly for the indication this drug is filing for but this drug may get used off label. I think there is a greater risk of anaphylactoid reactions occurring with administration of this product in patients who think once they have their first dose they can expose themselves to something they are either highly allergic to or anaphylactoid to.

And it is clear from other data that you have to wait at least six to eight weeks for the already mast cell-bound IgE to dissipate before exposure is safe.

I think somehow that needs to go into the product labeling that the first dose of drug doesn't get you protection from your anaphylactoid reactions that may already be preexistence. I think statistically we are far more likely to see anaphylaxis in that setting.

MR. MARKS: I don't think we have any data that this product can protect you from anaphylactic reactions to any other triggers.

DR. FINK: There is data with a similar product, at least in peanut anaphylaxis.

MR. MARKS: Yes, that is a different product.

DR. FINK: Right. I said it was different.

MR. MARKS: I think it's important for everyone to understand that those data are with regards to a different product and we really can't extrapolate between the two.

DR. FINK: Although I think it is clinically moderately likely there will be physicians in the practicing community when this product reaches the market who will have read some of the other data and may use this off-label for peanut anaphylaxis.

CHAIRMAN PARSONS: But again, to reiterate, for this product there has been no data presented today regarding that.

DR. FINK: Real world.

CHAIRMAN PARSONS: I think we can move on to question No. 8 unless there are further comments or discussion.

8) A few published reports suggest IgE may have a role in mucosal immune function. Altered mucosal immunity may lead to adverse events. Although no excess in respiratory system adverse events was observed, there was an overall increase in digestive system adverse events in omalizumab treated patients compared to control patients.

These encompassed a variety of specific types of events. The rate of appendicitis was slightly higher in the omalizumab group. Also observed was a small increase in the rate of female genitourinary adverse events, without any specific type of adverse event of increased frequency.

Please discuss the importance of these events within the overall safety profile of this product.

CHAIRMAN PARSONS: Dr. Apter.

DR. APTER: These events mostly came from

the uncontrolled trials. Did they not?

CHAIRMAN PARSONS: Can the agency answer that question?

DR. RIEVES: No, these are from the all-controlled studies. This includes the open-label studies.

DR. APTER: It includes the open-labeled. Right. So I think we need blinded studies or just observation in the future when people know what study assignment they have, what drug they're getting and they no it's active drug.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: I was very unimpressed by this group of concerns personally. You know, you would want follow-up once it's released and certainly it could turn out to be something but I was not impressed by any of this group of concerns.

CHAIRMAN PARSONS: Other committee members? Dr. Fink.

DR. FINK: I think this is a fascinating question for some basic science researchers but I really don't see where it has anything to do with

approval of the current product. It raises an interesting question does IgE have an immune function that we have not previously attributed to it. I really think that is a basic science question that doesn't really particularly bear on approval of the product.

CHAIRMAN PARSONS: Other committee members?

Just before we leave this specific topic, one of the other questions that came up earlier in the IgE realm and sort of what does it do was the question about parasitic infections which there is now a study going on in Brazil. Are there any other considerations of patients who we would consider in our practice that maybe going places, doing things that could expose them to something that would be an issue?

I can't think of any. I'm just throwing this out to complete this one area. What about patients with known mucosal abnormalities in terms of any issues there. I think that is a great unknown. I'm just asking. Dr. Fink.

DR. FINK: I mean, you could hypothesize that you would be a bit concerned about IgA deficient patients which are fairly common occurring in about one in 1,000 or one in 1,200 who often do have elevated levels of IgE but I have no idea what the problem is. They also have an increased incidence of asthma. If you are IgA deficient and your IgE is elevated, you are more likely to wheeze for some reason.

Whether that puts your mucosal surfaces at any increased risk, I'm not sure. We do see in those instances that it is clear in those children, otitis media, sinusitis early in life, at least, are markedly increased in incidence, although in adulthood most people who are IgE deficient don't know it.

CHAIRMAN PARSONS: Additional comments? Dr. Dores.

DR. DORES: I would just point out that patients with IgA deficiency also have increased risk of transfusion reactions. Just keep that in mind.

CHAIRMAN PARSONS: Were there other specific questions related to any of the specific adverse event issues that the agency had?

MR. MARKS: No. I think that you have covered many of our questions already. Thank you.

CHAIRMAN PARSONS: Ready to go on to question No. 9.

9) Certain aspects of the submitted safety database may place limitations on the interpretation of the results. For example, comprehensive data are limited to one year of omalizumab exposure. Additionally, the database contains only approximately 150 geriatric subjects treated with omalizumab.

a) Please discuss the importance of these limitations, and whether safety concerns with regard to these aspects specifically warrant obtaining additional data. If so, please identify which specific areas require more information.

b) Please discuss if these or other limitations or findings may necessitate the submission of additional data from the applicant

prior to being able to form a risk-benefit assessment.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: I've said this before. I think for the group over 65 that the efficacy data was poor. In this case I thought the general concerns of whole body side effects were higher. They are at bigger risk for cancer. I just think that group needs to be specifically studied in a real double-blind placebo controlled study like was done before that group was allowed to get this drug or biologic.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: I would echo those remarks and say maybe they should also be -- that should also include individuals between 12 and 16 years of age where there is similarly a lack of data in terms of safety or efficacy.

CHAIRMAN PARSONS: Ms. Schell.

MS. SCHELL: I have a question on what percentage of asthmatics are over 65? Is there any information on that?

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: The data that I've seen suggest that it's just as common actually in adults over age 65 as in other adults which is in the 8 percent or so prevalence range.

CHAIRMAN PARSONS: Additional concerns regarding different groups? The two groups that have been mentioned are the geriatric, over age 65 population, and the age 12 through 17. There were concerns earlier, if I recall, about age 5 through 12. Is that correct?

DR. APTER: And minorities. We had discussed this before.

CHAIRMAN PARSONS: That was my next question. That was the other area that we had addressed previously. Were there specific study design questions that the agency had regarding these groups?

DR. WEISS: I just wanted to ask this group a question and I would start with the 5 to 12 year-old group. You know, the company is not asking for its use to be extended down to the pediatric. They are asking down through adolescence but not to

the pediatric age group.

What generally happens is people are probably very familiar in terms of when studies are done in a disease that is common in adults but also seen in children, often times there are no studies done ad products just tend to get used a lot in pediatric populations and over time the physicians just develop experience with this.

This is a little different in the sense that we actually do have a trial in the younger children, trial 010. It did show some similar results.

I don't want to speak for the company but, you know, a lot of unknowns with the new therapeutic and things that were even raised around the table here, potential for long-term use and what impact it might have on development of malignancies over time, lymphoproliferative disorders, etc.

For many products if you're talking about long-term use in a very young population for a non-life threatening or immediately life-threatening disease, often times there is the thought that

prudence is better and to wait and get more adult safety data in particular before use in children.

I was just wondering from the committee often times we provide in the label what data we have. We can also sometimes in the label under pediatric use section describe particular concerns, precautions, anxieties. For instance, you know, concerns about malignancies, etc.

Does the committee have any advice? Levels often times say either safety and efficacy have not been studied in children, which would not be true in this case. We could say safety and efficacy have not been established which might be more the case.

Those tend to get ignored if people want to use products in different age populations. Physicians, of course, are free to use any product as they see fit in the practice of medicine. I'm just wondering if there is specific advice we could provide to physicians, particularly ones who have a pediatric asthma population.

We heard it's hopefully being evaluated

further but if this product is approved, and we'll get to your recommendations in a minute in question 10, whether or not there is specific advice you can give us on what to say on a label with respect to younger children, the 5 to 12, and then again the 12 through 17 years of age in terms of what's known, what's not known, what are the concerns. Sorry for the long question.

CHAIRMAN PARSONS: Dr. Atkinson.

DR. ATKINSON: I would like to say that I don't have anymore concern in the younger patient age range than I do about the older age ranges. I think it is likely to be because allergic asthma is so prevalent in that age range I think it's likely to have at least equal efficacy. I don't think you have to worry too much with a product that is going to be this expensive about too much off-label use in younger age groups.

I may be wrong but I think if they are not able to obtain help from insurance companies and so forth it's not likely that children are going to -- a lot of children are going to get treated with this

unless it's approved. I may be mistaken. I'll see what other people think.

DR. WEISS: I want to clarify that oftentimes when we write an indication statement sometimes we say it's indicated for adults with or adolescents or adults with.

Sometimes we say it's indicated for patients with this disease and then we describe elsewhere in the label what's known or not known about the different subgroups of the population. There's different ways that one can try to help provide guidance in terms of who products should be indicated for.

Some of that bears upon, I think, what people think in terms of who best should -- if this is recommended for approval who best would benefit and where it should perhaps be used until further data are available.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: Again, I think there is a consensus that we probably wouldn't want it used in patients over age 65 until more data is available.

On the other hand, we would like more data available for minorities but I don't think we would want to say don't use it until then. At least, I haven't heard that.

I just want to revisit one other issue, the issue of the efficacy in the adolescents 12 to 18. The only definite -- the things that I can find easily are table 85 and 86. In table 85 the exacerbation rate in the drug were 10 percent versus 24 percent in placebo. Although the rate difference cross zero, that seems to be respectable.

That is in the stable steroid phase and it was a significant change similar to other ones in the steroid reduction phase. I wonder what other information is available to give the impression, which I must say I didn't have, that it was really substantially less effective based on the data in 12 to 18 year olds.

MR. MARKS: I don't believe we really do have any data that there is a differential and efficacy. Certainly I don't believe we presented anything that was trying to suggest that.

DR. APTER: I made a comment earlier but I just meant numbers. There were small numbers, not efficacy differences.

CHAIRMAN PARSONS: Yes, the numbers have been brought up a couple times, relatively small trial.

DR. WEISS: To some extent sometimes you do have smaller numbers obviously in certain subgroups but one just generalizes down from the overall population or the larger population of 18 through adults down. It's a question of are there higher numbers in the adolescent population that you feel you would prefer to see before suggesting that this might be used in that population.

CHAIRMAN PARSONS: Dr. Fink.

DR. FINK: I think a commitment to at least a early Phase IV safety study in children five to 16 is important. We really need to know are there any difference signals there. It needs to be a controlled trial before too many patients are exposed because it is definitely going to get used in that age group in patients with allergic asthma

whether it's labeled or not.

I think the sooner that data becomes available -- again, we're getting into the classical pediatric conundrum of a drug that appears effective and then starts getting used in kids without good safety data.

On the benefit side, this is a drug that theoretically I would think if you followed adult dosing guidelines they would not be any different in pediatric patients. I don't think IgE levels or body weight are inherently different in kids. Immunoglobulin half-lives are clearly not different in children above age five. At least dosing may not be as big an issue but safety clearly should be studied.

CHAIRMAN PARSONS: What about dosing in terms of -- I mean, kids change weight even more quickly than some adults do and changes in IgE levels as they age. How does that -- do you have any suggestions on how that might work?

DR. FINK: Weight is pretty easy. I mean, as a pediatrician I'm used to adjusting dosages by

weight all the time and whether you use five-pound increments or 10-pound increments or dosage increments in terms of the capsule size. It's not particularly burdensome.

The IgE level is much more difficult because I don't know how you assess it without stopping the drug.

CHAIRMAN PARSONS: Are there any additional comments or questions overall before we get to question No. 10? Do any members of the committee have additional questions for anybody? Additional areas of discussion that have not come up or that have not been clarified? This is a remarkable placid group right now. That's good.

MR. MARKS: I think you have very adequately discussed the questions we've put before you.

CHAIRMAN PARSONS: We've been asked then to take a specific vote on question No. 10 which is:

10) Do these data indicate a favorable risk benefit comparison for omalizumab?

All the voting members will be asked to

vote on this. I think the question is in a way two-fold. One is, is there a favorable risk benefit comparison in your opinion. The other is for whom or what patient population. I think we should clarify.

We will go around the table and each person will give their opinion. Number one, if they could say do they think there is a favorable risk benefit and, number two, can they clarify which patient population they are talking about. We'll take it that way.

I'm going to start at this end with Dr. Morris who has been in the committee before.

DR. MORRIS: Yes, I would say there is evidence today presented for favorable risk benefit overall for this drug or biologic. I think to help identify the population, the population identified that in the two pivotal studies 008 and 009, those identified by skin testing with the IgE levels that are appropriate. I think for what we're talking about, what has been talked about in regards to age, I think less than 65 would be important as well.

CHAIRMAN PARSONS: Do you want to comment further in terms of patient inclusions? There were issues that came up regarding inhaled steroids or all steroids.

DR. MORRIS: I think all steroids would not be in the population that I would recommend.

CHAIRMAN PARSONS: Dr. Joad.

DR. JOAD: Yes. I would vote yes about the benefit risk as to the positive. I also have my age range 12 to 65 with allergic asthma to be defined as at least one positive test to a perennial aeroallergen. I would like them to have failed the NIH guidelines to be included.

Personally, I don't have a problem with -- I would like there to be a study on the oral steroids but I wouldn't think that at this point there's enough evidence to say they shouldn't receive it. It's a group that people are going to want to use it in.

CHAIRMAN PARSONS: Dr. Chinchilli.

DR. CHINCHILLI: Yeah, I agree with Dr. Joad. I would say yes, age range 12 to 65. I'm

also concerned about the group on oral steroids since they are the most severe and desperate group. I would hate to see them excluded.

CHAIRMAN PARSONS: Dr. Atkinson.

DR. ATKINSON: Yes, I agree that the indication for allergic asthma and ages 12 to 65 with a recommendation that skin tests be performed to try to establish that the asthma actually is associated with atopy.

CHAIRMAN PARSONS: I too would vote yes. I would also have a specific age range of 12 to 65. I would request that the patient carry a diagnosis of allergic asthma that involves appropriate skin testing and have relevant IgE levels for dosing.

I would suggest that it is most efficacious in people on inhaled steroids. I do not necessarily have problems with people on oral steroids taking it but I think it should be clear that there is no data that shows significant efficacy mean data in that patient population.

Dr. Apter.

DR. APTER: I would vote yes. Certainly

the upper limit would be age 64. I'm a little concerned about below age 18 because of the small numbers. I do think selection should be based on skin test and history for a diagnosis of allergic asthma.

I'm concerned, though, about long-term effects of the drug and think it is essential that the people on drugs be followed carefully over time in Phase IV and even they stop the drug.

I would certainly favor a trial that compared Xolair and inhaled steroids with inhaled steroids and long-term beta-agonists or some trial that compares the use of Xolair to our current best effective therapy now.

I would not exclude smokers and I do think that Phase IV studies and continued exposure should be -- studies should be done with an eye to determining how long this therapy should go on.

CHAIRMAN PARSONS: Thank you. Dr. Fink.

DR. FINK: I would vote yes. It has shown efficacy, at least in the age range 12 to 65, although I'm pretty soft on the cut-off at 65.

Although there is not enough data there, I am not sure that we should necessarily exclude that group which often has asthma that is more bothersome, particularly for individuals who are barely independent because of their age.

They may actually have more clinical benefit in some ways than some of the younger patients. At least 12 to 65 but I'm not sure I would object to extending it beyond age 65 based on the presumption of efficacy and not being convinced there is significant additional toxicity in that age group.

I think the package insert has to be carefully worded and contain as much data as possible knowing that most people in practice won't read it. I think they should still have access to the data if they will read it because some of these issues are not obviously clear cut and the best you can do is provide what data exist.

CHAIRMAN PARSONS: In addition to the age range were there other qualifications in the patient groups?

DR. FINK: No.

CHAIRMAN PARSONS: Dr. Schatz.

DR. SCHATZ: I would vote yes assuming the population is limited to those not controlled on inhaled -- this is going to sound familiar but not controlled on inhaled steroids. I would add, though, with a baseline FEV1 less than 80 percent as another way to define inadequate control and because that's what all the data really suggested where efficacy was and where most of the patients were studied.

I would want specific IgE determined either in vitro or by skin test but it would be to a perennial aeroallergen to which the patient was chronically exposed. I would also go for the 12 to 64 age range and I would include no prior history of cancer except non-melanoma skin cancers.

CHAIRMAN PARSONS: Thank you. Ms. Schell.

MS. SCHELL: I would vote yes also and I would like to include patients up to 65 but not exclude the over 65 with more data. Also I think it should be given to smokers as well. If there is

data available for that in the future, I would like to see that.

Also the steroid dependent -- oral steroid dependent. I would like to see a bigger group studied on that and comparative study to the controller medications that are currently available as to the benefit if you can decrease one and just be on one drug.

Also, I would like to see -- I lost my thought there. Just a second. I would like to see more information regarding the younger children as to if it's beneficial or not.

Also a clear definition of what is allergic asthma because most physicians that I work with don't differentiate between allergic and nonallergic and I think there needs to be clearer guidelines if they are going to administer the drug as to what constitutes allergic asthma. Also I like the FEV1 objective measurement.

CHAIRMAN PARSONS: Thank you. Dr. Swenson.

DR. SWENSON: I vote yes for that age

group of 12 to 65. Of course, this would all be contingent on positive skin testing or appropriate in vitro lab testing. I would strongly urge that patients with any history of malignancy.

Although we didn't discuss it, I wonder about patients that are immuno-compromised beyond just their steroid therapy for asthma to be possibly considered. And that there be strong commitment to Phase IV follow-up for many of the identified possible at-risk groups that we have discussed here.

CHAIRMAN PARSONS: Thank you. Dr. Dores.

DR. DORES: I think at present there is an apparent risk benefit, favorable risk benefit profile. I do want to underscore a large caveat about the incidence of cancer with this drug. I think we just don't know and that needs to be clearly defined.

And people should be aware that has not been adequately studied simply because of inadequate time. I feel very strongly about that. People who are treated with this medication need to be followed. I feel very strongly about that as well.

I would have some reservation about giving this medication to immuno-compromised individuals. I think I defer as far as pulmonary guidelines because I feel really that's not in my area of expertise.

CHAIRMAN PARSONS: Thank you. We've heard from all the voting members of the committee. The vote is 11 yes and none no. No nos. I think a number of the committee members have had fairly specific caveats to clarify their yes vote.

Mr. Ohye.

MR. OHYE: Excuse me. I have been asked by some industry colleagues and, in particular, your regular industry representative to acknowledge four members of this committee that will be leaving with this meeting and to thank them for their service and to say that I know they are advisors to FDA.

Their observations and service over the years has been extremely useful to industry as a whole and their ability to admire how to balance the need for good science against the fact that there are patients like Dr. Ainbinder and Mr. Vallejos

waiting for a new medicine was very important to us. Thank you all. Best wishes and God's speed.

CHAIRMAN PARSONS: Thank you. Are there additional comments from the agency?

MR. MARKS: No, I don't think we have any additional questions. I would like to thank all of you very much for coming and struggling with these questions and giving us advice on how to proceed. It is extremely valuable and to hear the diversity of opinions and the expertise that you all bring to this will make our job much easier. Thank you.

CHAIRMAN PARSONS: I thank all the committee members and I would like to go on record as apologizing for not being able to pronounce the name for Xolair and to reiterate that I cannot pronounce any of the antibody drugs. I could not be a cardiologist in this day and age. I apologize. It's not specific to this one.

Thank you again.

(Whereupon, at 4:00 p.m. the meeting was adjourned.)