FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC)

Wednesday, December 9, 2015

8:00 a.m. to 3:44 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. OWNBY: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices that might make too much racket while we're here, if you've not already done so. I'd also like to identify the FDA press contact, Kristofer Baumgartner. If you're here, please stand up. There in the back, if you have questions.

My name is Dennis Ownby. I'm the chairperson of the Pulmonary-Allergy Drugs Advisory Committee, and I will be chairing this meeting. I will now call the Pulmonary-Allergy Drugs Advisory Committee meeting to order. We'll start by going around the table to introduce ourselves. I will start with the FDA on my left and go around the table.

DR. ROSEBRAUGH: Good morning. I'm Curt Rosebraugh, director, Office of Drug Evaluation II.

DR. CHOWDHURY: Good morning. I'm Badrul Chowdhury. I'm the director, Division of Pulmonary, Allergy, and Rheumatology Products.

DR. KARIMI-SHAH: Good morning. My name is Banu Karimi-Shah. I'm a clinical team leader in the same division.

DR. DONOHUE: Good morning. Katie Donohue, medical officer in the division.

DR. PEDRAS-VASCONCELOS: Good morning. I'm Joao Pedras-Vasconcelos, the immunogenicity reviewer from Office of Biotechnology Products.

DR. PLATTS-MILLS: I'm not at the FDA. I'm Tom Platts-Mills. I'm at the University of Virginia. I've been studying immunogenicity for a long time.

DR. VOYNOW: I'm Judy Voynow from Virginia Commonwealth University. I'm in pediatric pulmonology.

MS. HOLKA: Good morning. Andrea Holka. I'm the patient rep.

DR. TRACY: Jim Tracy, Creighton University, Omaha, Nebraska, and I'm an allergist/immunologist.

LT. HONG: I am Cindy Hong, the designated federal officer for the Pulmonary-Allergy Drugs Advisory Committee.

DR. OWNBY: Dennis Ownby from the medical college of Georgia at Augusta University.

DR. GEORAS: Steve Georas, University of Rochester, New York. I'm an adult pulmonary and asthma.

DR. WEBER: Dick Weber. I'm at National Jewish Health in Denver, Colorado, and I'm an allergist.

DR. MORRATO: Good morning. Elaine Morrato. I'm an epidemiologist and health services researcher from the Colorado School of Public Health.

DR. CONNETT: I'm John Connett. I'm a biostatistician at the University of Minnesota.

DR. YU: Good morning. Yanling Yu, research scientist at the University of Washington, and I'm a consumer rep.

DR. STOLLER: Good morning. Jamie Stoller. I'm with the Cleveland Clinic. I'm an adult

pulmonary critical care doc.

DR. GREENBERGER: Good morning. Paul Greenberger, Northwestern University, Division of Allergy-Immunology in the Department of Medicine.

DR. DYKEWICZ: Good morning. Mark Dykewicz, St. Louis University, allergy, immunology, in the Department of Internal Medicine.

DR. BRITTAIN: Erica Brittain. I'm a statistician at National Institute of Allergy and Infectious Diseases, NIH.

DR. COOK: Jack Cook, acting industrial representative, clinical pharmacology with Pfizer.

DR. OWNBY: Thank you.

For topics such as those being discussed in today's meetings, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for the discussion of these issues and that individuals can express their views without interruption. Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We

look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about topic at hand take place in the open forum of this meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass it to Lieutenant Cindy Hong who will read the conflict of interest statement.

Conflict of Interest Statement

DR. HONG: The Food and Drug Administration is convening today's meeting of the Pulmonary and Allergy Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry

representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information of the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's

meeting, members and temporary voting members of this committee has been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves biologics license application 761033, reslizumab, for injection submitted by Teva Pharmaceuticals Industries for the proposed indication to reduce exacerbations, relieve symptoms, and improve lung functions in adults and adolescents 12 years of age and above with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.

This is a particular matters meeting during which specific matters relating to Teva's biologic license application will be discussed.

Based on the agenda for today's meeting and

all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Jack Cook is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Cook's role at this meeting is to represent industry in general and not any particular company. Dr. Cook is employed by Pfizer.

I would like to remind members and temporary voting members that if the discussions involve any other products or firms already on the agenda for which an FDA participant has a personal or an imputed financial interest, the participants need to exclude themselves from such involvement, and

the exclusion will be noted for the record.

FDA encourages all the participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. OWNBY: Thank you.

We'll now proceed with the FDA's introductory remarks from Dr. Karimi-Shah.

FDA Opening Remarks - Banu Karimi-Shah

DR. KARIMI-SHAH: Good morning. My name is Banu Karimi-Shah, and I'm an adult pulmonary and critical care doctor. And I work as a clinical team leader here in the Division of Pulmonary, Allergy, and Rheumatology Products at FDA.

On behalf of all of my colleagues, I'd like to welcome the pulmonary advisory committee members to the meeting today. As members of the FDA advisory committee, we consider your expert scientific advice and recommendations and important component to our regulatory decision-making process.

I want to thank you for your preparation in

advance of this meeting and your attendance and participation today. We look forward to the discussion and feedback you will provide. I'd also like to extend a special thanks to Dr. Ownby who's presiding as chair over the meeting today.

The purpose of today's meeting is to discuss the new biologics licensing application, or BLA, submitted by Teva Pharmaceuticals for Cinqair, or reslizumab, administered via intravenous infusion for severe asthma.

As is typical of our advisory committee process, we will ask the committee to discuss the overall efficacy and safety of reslizumab. In addition to those issues which the committee feels warranted targeted discussion, the agency puts forward the following issues that have been identified thus far during our review regarding which we would appreciate further input and consideration from the committee.

The issues are listed here to highlight them for you as you listen to both the sponsor and FDA presentations throughout the morning. The first

issue on this list is the adequacy of dose ranging and dose selection in the clinical development program. Second is the adequacy of the collected safety data with respect specifically to anaphylaxis and muscle toxicity. Finally, we ask you to consider the risk-benefit assessment in patients 12 to 17 years of age.

After I present some background slides and introduce the clinical development program, I will present a high-level overview of each of these issues for consideration.

Reslizumab is a humanized monoclonal antibody of the IgG4 kappa subtype, which binds to IL-5. IL-5 is the main cytokine involved in the regulation of blood and tissue eosinophils.

The proposed dose and route of administration is 3 milligrams per kilogram via intravenous infusion once every 4 weeks. For the purposes of this advisory committee meeting, the target population for this therapy is a severe asthma population.

You will see that the verbatim indication

statement that was cited in our briefing documents and in the Federal Register notice for this advisory committee meeting is not shown here on this slide. This is because the exact wording of the indication, should this product be approved, is an active review issue, and the sponsor has committed to working with the agency to come up with the most appropriate indication.

That said, the agency acknowledges that reslizumab, if approved, will be directed to a targeted patient population with severe asthma, similar to the population studied in the pivotal efficacy and safety trials. The proposed age range of the target population is patients 12 years of age and older.

Reslizumab is not currently marketed in the U.S. or any other country in the world. If approved, it would be the third monoclonal antibody to be approved for asthma with omalizumab, an anti-IgE, being the first, and mepolizumab, another anti-IL-5, which was recently approved on November 4, 2015 and discussed at a

Pulmonary-Allergy Drugs Advisory Committee meeting on June 11, 2015.

Mepolizumab is approved as add-on maintenance treatment of patients with severe asthma age 12 years of age and older and with an eosinophilic phenotype.

The basis of mepolizumab approval was a reduction in asthma exacerbations, oral corticosteroid sparing, and a trend towards improvement in asthma symptoms. If approved, reslizumab would be another choice in the class of anti-IL-5 agents.

Despite having several products approved for the long-term maintenance treatment of asthma, therapeutic challenges remain in the management of severe asthma. It is estimated that about 5 percent of the asthma population have severe asthma with an eosinophilic phenotype despite being on maximum therapy, and many of these patients are on oral corticosteroids and are still uncontrolled.

Patients with severe uncontrolled asthma are more likely to experience frequent asthma

exacerbations and hospitalizations because of asthma. Thus, development of safe and effective therapies targeted to this subpopulation is an important therapeutic step in improving asthma outcomes.

In the upcoming presentations, you will see that the clinical program in asthma primarily consisted of the five studies as listed on this slide, studies 3081, 3082, 3083, 3084, and 3085.

Study 3081 was a 16-week dose-ranging study in the asthma population, including two treatment arms of 0.3 and 3 milligrams per kilogram intravenously given every 4 weeks of reslizumab as well as a placebo arm with lung function measured by FEV1 as the primary endpoint. This is the only asthma study to evaluate more than one dose in the pivotal program. I will speak more about this study subsequently.

Studies 3082 and 3083 were 52-week studies, which evaluated frequency of exacerbation as their primary endpoint. Study 3085 was an open label safety extension with patients rolled over from

studies 3081, 82, and 83.

Studies 3081, 82, 83, and as a result, 85, all enrolled patients with persistent asthma with blood eosinophil counts greater than or equal to 400 cells per microliter. Study 3084 allowed any blood eosinophil count and was specifically designed to assess whether there was a treatment interaction between lung function and eosinophil count.

You will hear about each one of these studies in greater detail throughout the course of the morning. I will now go through each of the issues for consideration that I mentioned earlier in a high-level summary. Let's begin with the adequacy of the dose ranging and dose selection in the clinical development program.

Study 3081 was a 16-week lung function study. This was the only study to evaluate more than one dose in the intended patient population, 0.3 milligrams per kilogram and 3 milligrams per kilogram given intravenously every 4 weeks. The primary efficacy endpoint was overall change from

baseline in trough FEV1.

As you listen to the presentations this morning, I would like to highlight the following issues for your consideration.

Study 3081 was conducted essentially concurrently with the pivotal exacerbation studies. Therefore, this study did not inform the dose of 3 milligrams per kilogram carried into the exacerbation studies. The higher dose was chosen based on the ability to maximally reduce blood eosinophils.

While the reduction in blood eosinophils is greater with the 3 milligram per kilogram dose, as you will hear in the presentation this morning, it is notable that efficacy with respect to lung function was statistically superior to placebo for both doses. Importantly, while the treatment difference is numerically higher in the 3 milligram per kilogram treatment group, there was no statistical difference between groups.

As the subsequent efficacy discussion will detail and both the sponsor and the agency will

present, reslizumab 3 milligrams per kilogram appears to have demonstrated efficacy with respect to exacerbation in studies 3082 and 83. However, based on the limited dose-ranging data available, it is unclear whether a lower dose might have been effective as well.

The question of what is required of dose-ranging studies and ultimately dose selection is one that often comes up in our conversation with sponsors. I display the efficacy standard for approval from the Code of Federal Regulations here. We have interpreted this regulation to mean that applicants should select a dose that is scientifically justified and not necessarily a dose that is on the plateau or extreme right of the dose-response curve.

However, the adequacy of dose selection must also be considered from a safety perspective. We often advise sponsors that the study of multiple doses is prudent. In the event that safety signals are noted with higher doses, data will be available for potentially effective lower doses for which the

safety signals may not be seen.

As an example, for inhaled corticosteroids, we often see development programs explore doses over at least a twofold range in an effort to get a dose that is optimally positioned on the dose-response curve so as to minimize the dose and avoid adverse effects.

In the reslizumab development program, we are concerned about two serious safety signals in particular: anaphylaxis and muscle toxicity with elevated CPK. The mechanism behind these two safety findings is unclear.

One potential issue that has arisen is the presence of alpha-gal, which you will hear more about in the presentations this morning. Reslizumab is manufactured in a murine NSO cell line, which synthesize a blood group oligosaccharide, galactose-alpha-1,3-galactose, also known as alpha-gal. Reslizumab does contain alpha-gal, and this moiety has been implicated in anaphylaxis with other drug products.

Whether and to what extent alpha-gal is

playing a role in the observed safety signal is unclear. The sponsor will present some new data today that may call the alpha-gal hypothesis into question. However, the signal is still present, and the agency has not had the opportunity to review these data, and thus the rule of alpha-gal does remain an open question.

While the mechanism behind anaphylaxis can often be a mystery and classic anaphylaxis is not typically dose related, other safety findings are often considered dose related. We ask the committee consider carefully the dose-ranging data and rationale for selection of the 3 milligram per kilogram dose to determine whether this is adequate from a safety perspective, whether we have insufficient information to make a determination, or whether additional dose-ranging data should be required, keeping in mind that there is a tenfold difference between the doses studied and the lower dose did show efficacy in terms of lung function.

It is important to keep in mind the safety standard used to decide whether an application

should or should not be approved for marketing. Here you see displayed the safety standard. The three criteria include that the application do not include adequate tests to show whether the drug is safe, the results of these tests show that the drug is unsafe, or that there is insufficient information about the drug to determine whether the product is safe.

Fulfillment of any of these three criteria may be grounds upon which the safety standard is not met in order to approve an application. Keeping this in mind, I'd like to revisit the safety signals of anaphylaxis and muscle toxicity.

Anaphylaxis is a known risk with biologic drug products. In this development program, it was identified by investigators and reported as an adverse event, but it was not prospectively evaluated according to accepted clinical guidelines. Typically, the agency has used the NIAID/FAAN criteria published by Sampson, et al. in order to identify cases of anaphylaxis.

Because there were cases reported by

investigators, the agency asked the applicant to retrospectively adjudicate these cases. This is a suboptimal mechanism to identify cases especially in the setting of this application, as all data necessary to make a determination were not uniformly collected or available in order to generate the cases for review. For example, post-dose vital signs were not uniformly collected.

Unlike anaphylaxis, CPK elevation is not a known safety signal with biologic drug products, so the appropriate collection of data is now raised in hindsight. In support of the muscle toxicity signal, however, is that the CPK elevation was accompanied by various muscle symptoms that were increased in reslizumab-treated patients.

While this was not an expected effect of the drug or the class of drugs, and hindsight is often 20/20, the evaluation was not done in a way that would have identified the magnitude of toxicity because muscle enzymes were predominantly checked before the next dose was given and not post-dose.

Since much of the knowledge we have about

CPK elevation comes from examples in small molecules like the statins, for example, it is unclear if the true magnitude and nature of the toxicity has been established.

Based on the limitations in the way these two safety signals were evaluated, we ask the committee to recall the safety standard I displayed earlier and engage in a discussion as to whether these two very important safety signals have been adequately evaluated and whether, with respect to these two safety signals in particular and the program as a whole, there is sufficient information to inform the safety of reslizumab for its intended use in the proposed asthma population.

Lastly, we ask that the committee specifically consider the risk-benefit assessment in pediatric patients. You will see some data today that the efficacy data in the pediatric subgroup showed a less robust response with respect to exacerbation in FEV1 with point estimates favoring placebo. Understanding the limitations of subgroup analyses and that the studies are not

powered to show an effect in subgroups, because pediatric patients are considered a vulnerable patient population, this consideration is driven by the safety signals observed in this program.

Based on this high-level overview of the topics I have outlined, there will be a total of five questions today, two discussion items on efficacy and safety and three voting questions regarding efficacy, safety, and approval. I will go over the questions in more detail in the charge to the committee later today.

I thank you for your attention. I now turn the meeting back to Dr. Ownby.

DR. OWNBY: As we move forward to the sponsor's presentation, I'd like to remind that both the FDA administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all

participants, including the applicant's nonemployee presenters, to advise the committee of any financial relationships that they may have with the application such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, the FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Teva's presentation.

Sponsor Presentations - Tushar Shah

DR. SHAH: Thank you. Good morning. My name is Tushar Shah, and I'm the senior vice president responsible for global respiratory R&D at Teva Pharmaceuticals.

I will serve as the moderator of our

presentations today. Before we begin, I would like to thank the FDA and the advisory committee members for their time and the opportunity to share the results of our development program.

Due to the limited time we have this morning, we have focused our presentations to address the questions before you in considering the approvability of reslizumab. All the information is also provided in our briefing document in much greater detail. We're also available to answer any questions the committee members have on the information we have provided.

Reslizumab is a humanized IgG4 kappa anti-IL-5 monoclonal antibody. IL-5 is an attractive pharmacological target because it plays a major role in the regulation of eosinophilic formation, maturation, recruitment, and survival. By reducing eosinophilic inflammation, treatment with reslizumab improves asthma control.

Reslizumab treats both current impairment such as symptoms and lung function, as well as future risk by reducing asthma exacerbations with

an acceptable safety profile. We believe that reslizumab addresses an unmet need for patients with elevated blood eosinophilia who continue to struggle with their asthma despite existing therapies.

Shown here is the proposed indication, which reflects the spectrum of asthma severity evaluated in the reslizumab development program. Teva will work with the FDA to ensure the indication reflects the patient population who can benefit most from this therapy.

With this in mind, the data from the clinical program, which we will review shortly, demonstrates that for asthma patients with elevated blood eosinophils who are inadequately controlled on an ICS-based regimen, reslizumab reduces exacerbations, relieves symptoms, and improves lung function.

In the next slide, we have tried to estimate the proportion of the U.S. asthma population that could benefit from such therapy. In order to arrive at this estimate, we have to use various

sources of epidemiology data since a single source to determine this estimate is not available.

Of the overall U.S. population shown in the large bubble, approximately 39 percent have more severe disease; and of these, approximately half would be expected to be inadequately controlled. Of the more severe inadequately controlled patients, approximately 16 percent would be expected to have an elevated eosinophilic driven disease.

This analysis leads to our estimate that approximately 3 to 4 percent of the U.S. asthma population could benefit from reslizumab therapy. These are the patients who continue to drive much of the morbidity and mortality in asthma as well as contribute to considerable healthcare cost. There is no question that these patients desperately need new therapies for the management of their disease.

I now would like to turn our attention to a description of the product and its manufacture. Reslizumab is produced as a sterile solution in a single-use vial that does not require

reconstitution. It is mixed with saline for IV infusion at a dose of 3 milligrams per kilogram every 4 weeks under the supervision of a healthcare professional.

Reslizumab is manufactured using a robust and validated process consistent with regulatory and industry standards. The same process was used for the phase 2/3 clinical trials that will be used for the commercial supply. This helps to ensure that the clinical data is representative of the efficacy and safety of the product when available commercially.

The process follows all relevant FDA and ICH guidance for production of monoclonal antibodies. Extensive quality control testing is done on every batch to ensure consistency and product quality.

Reslizumab contains low levels of galactose-1,3-alpha-galactose also known as alpha-gal. The cell line, which is used to produce reslizumab, NS0, is known to glycosylate proteins with alpha-gal. For this reason, FDA is raising as a topic for today's discussion the possibility that

the alpha-gal present in reslizumab may be responsible for the anaphylaxis cases seen in the asthma program. These cases will be described in greater detail in the safety presentation given by Dr. Shalit.

Alpha-gal is discussed in our briefing materials, and there are experts here today on the panel and with Teva who are available to discuss this further.

Alpha-gal is a mammalian oligosaccharide, which is regarded as foreign in humans. We are all exposed to alpha-gal in our diet by consumption of red meats. In fact, most of us have circulating IgG antibodies directed against alpha-gal. In sensitized individuals, an IgE immune response occurs. This sensitization seems to be associated with tick bites. These individuals can develop anaphylaxis with the consumption of red meats or exposure to biologic agents containing alpha-gal.

Upon review of the evidence, alpha-gal is unlikely to be associated with anaphylaxis with reslizumab. The reason for this conclusion is that

reslizumab has low levels of alpha-gal, which is only present on the Fc portion of the molecule. Other alpha-gal containing monoclonal antibodies, which are currently available on the market which have similar profile, have shown a low propensity to bind alpha-gal IgE and cross-link these antibodies bound to mast cells.

In addition, the clinical cases of anaphylaxis seen in the reslizumab program are not consistent with alpha-gal-related reactions. The reactions with reslizumab did not occur with the first infusion or were associated with a history of red meat or tick bites.

Finally, we recently received the results of anti-alpha-gal antibody levels from these patients using the commercially available assay. Since this information was recently submitted to the FDA, we acknowledge that they may not have had the opportunity to review the data.

All of the patient samples were negative for these antibodies, further supporting that alpha-gal is unlikely to be associated with the anaphylaxis

reported with reslizumab. A risk of anaphylaxis is known to occur with the administration of biologic agents, and in most instances, the mechanism of these reactions remains unknown.

Now, let's take a high-level look at the overall clinical program. The clinical development of reslizumab in asthma was based on a robust set of studies, which were conducted to industry standards using investigator sites across North and South America, Europe, Asia, and Oceania.

The initial set of studies in asthma were conducted more than 15 years ago, which were unsuccessful in demonstrating a clinical benefit despite the reduction of blood and tissue eosinophilia. These initial failures raised many questions on the role of eosinophils in asthma pathophysiology.

It was not until about a decade later, when studies done in a more select group of asthma patients with evidence of active airway eosinophilia, were we able to demonstrate the clinical benefits of anti-IL-5 therapy. The

insight gained from these studies led to the development of the phase 3 clinical program. This program was reviewed and agreed with the FDA.

In addition to the asthma program, reslizumab was also studied in other diseases associated with eosinophilia. This included a study in nasal polyposis, several large studies in pediatric eosinophilic esophagitis, where over 200 children had long-term exposure to reslizumab, many who were exposed for several years, and PK studies in healthy volunteers.

Across these various studies, approximately 2200 individuals have been exposed to reslizumab, providing a large database to assess safety.

The agenda for our presentation begins with a clinician's perspective of the unmet need in asthma and patients with elevated eosinophils. This will be done by Dr. Mario Castro, who is the Alan A. and Edith L. Wolff professor of pulmonology and critical care medicine and professor of medicine and pediatrics at Washington University School of Medicine. Dr. Castro also served as an

investigator for the phase 3 reslizumab program and is an investigator on the NIH severe asthma research program or SARP.

Dr. James Zangrilli from Teva will share the clinical efficacy results from the reslizumab program, followed by Dr. Yael Shalit, who will review reslizumab's clinical safety information.

Dr. Castro will then return to provide a clinician's perspective on the use of reslizumab in a clinical setting after which I will conclude our presentations with some closing comments.

In addition to the presenters, we also have several experts from Teva and externally who are available to answer questions you may have on reslizumab and its development. These individuals and their areas of expertise are mentioned on this slide.

I especially would like to introduce Dr. Franklin Atkinson who is a professor of medicine at Johns Hopkins Asthma and Allergy Center. Dr. Atkinson is available to answer questions with regards to anaphylaxis associated

with biologic therapies.

Both Dr. Castro and Dr. Atkinson are paid consultants to Teva, but otherwise claim to have no conflicts. I would like now to welcome Dr. Castro for his presentation.

Sponsor Presentation - Mario Castro

DR. CASTRO: Good morning. I'd like to thank the PADAC for their time today. I'm Mario Castro. I'm from Washington University in St. Louis, and I'm going to provide the clinician's perspective on the use of a biologic therapy such as reslizumab in the treatment of asthma and in particular, the role of the eosinophils.

Now, Teva did fund my being here today, but I have no stock in Teva or any other conflicts of interest.

I'll be discussing briefly these two topics. As introduced by the FDA and by Dr. Shah, there is a huge unmet need in these subset of patients with severe asthma. We'll talk about how this meets the goals of asthma therapy, and then secondly, we'll talk more about the role of blood eosinophils and

their relationship to asthma control.

First in terms of the unmet need, as introduced by Dr. Shah, there was a substantial number of patients in the U.S. that suffer from asthma, and this results in substantial morbidity and mortality as demonstrated by these statistics. And of this group, we're going to talk about a subset of these patients that are not achieving asthma control that result in this morbidity.

This is best characterized by a prospective epidemiologic study called the TENOR study, and in the TENOR study, there was almost 5,000 patients that were prospectively followed over a three-year period of time at baseline and every six months. And like many of my patients, these patients were on multiple medications, as demonstrated here, 56 percent on three or more medications.

Despite them receiving the standard of care, these patients are still suffering a substantial morbidity from their disease. Sixty percent required oral steroid burst, and we know that these patients hate the oral steroids; 20 percent had

emergency room visits; and 10 percent were hospitalized. Because of this, these patients consume a disproportionate amount of the healthcare cost.

Recently, at the American College of Allergy, these results from the TENOR study were confirmed in a extension, the TENOR 2 study, again confirming, even in this year in 2015, that these patients with severe asthma have substantial morbidity.

Now, I know that you're all very familiar with the National Asthma Education Prevention Program guidelines, but I'd just like to review two key aspects of this in terms of reducing impairment and reducing future risk and how reslizumab potentially fulfills those criteria.

In terms of reducing current impairment, we want to reduce our patients' symptoms, their use of short-acting beta agonist. We want them to maintain or achieve near normal levels of their FEV1 and maintain normal level activities as well as meet their expectations.

But we also want to reduce future risk, and this is certainly a limitation of our current therapy. And we want to prevent recurrent asthma exacerbations and prevent that progressive loss of lung function that occurs while avoiding the adverse effects of the current therapy that we have to treat our patients.

I'll next talk about the role of elevated blood eosinophils and its relationship to asthma control. And first, IL-5, as we know, is a key cytokine that's responsible for eosinophilic maturation, survival, and activation. We know that the eosinophils have been highly implicated and studied over several decades in terms of its role in asthma pathogenesis. Therefore, inhibiting IL-5 is really an attractive pharmacologic target to treat patients with eosinophil-mediated asthma.

Now, as demonstrated in this diagram, the eosinophil has a key role in terms of asthma pathogenesis, in particular in our patients with difficult to control asthma, but also has a number of side effects on a number of other inflammatory

cells that we know are important in asthma. This includes, in effect, of course, on the bone marrow, effect on the B cells, T cells, neutrophils, macrophages, mast cells, and dendritic cells. So even though we're just inhibiting this one cell, there are a number of other downstream effects that occur in our patients once we inhibit the eosinophil.

In addition, this is probably one of the most well studied asthma phenotypes that have now developed in our current attempt to come up with targeted therapy. We have now identified that about 30 to 40 percent of our patients, depending on how you define it, have this eosinophilic phenotype with severe asthma.

I'd next like to introduce what we're approaching and what is probably the best studied biomarker that we have right now for severe asthma, and that's the role of the blood eosinophil.

Over a number of couple decades, we have been focusing on the role of airway eosinophils as measured by the sputum or as measured by

bronchoalveolar lavage or biopsy. And we've shown that certainly the eosinophil in the airway is a key player in terms of the pathogenesis of this disease. And now, what we have come back to is that actually the blood eosinophil count is an important player as a biomarker to identify those patients with sputum eosinophil.

I present these two meta-analysis, which are very recent, this past year, that summarize the various levels of sensitivity and specificity depending on which blood eosinophil cutoff you use. And as demonstrated here, once you reach a cutoff approximately of 400, you actually achieve quite high specificity, in the range of 95 to 97 percent.

This then allows us to have a very simple test that clinicians can use, no matter where they come from, to treat our patients and to identify those patients that have this eosinophilic phenotype.

What are the consequences of having high blood eosinophils and why is this an important or very important surrogate marker? And as

demonstrated here, we now know that as one looks at those patients with lower lung function, that there is this clear association with elevated eosinophils.

In fact, if you look at that cutoff of 0.4 on this graph, you'll note that most of these patients are below an 80 percent cutoff in terms of lung function. So therefore, certainly there's association between blood eosinophil counts and lung function.

But more importantly is what is the consequence for our patients is that we also know that the blood eosinophil level is important in terms of exacerbation, the future exacerbation risk as we talked about earlier with the NABP guidelines.

As demonstrated here in this recent review by Zeiger and colleagues, in this recent claims data analysis that was done by Zeiger and colleagues, as you look at increasing cutoffs of eosinophil level, that once you reach greater than 400, there is an increased risk of exacerbations in

the subsequent 12 months. And this corresponds to a rate ratio of about 1.3 or about a 30 percent increase in exacerbations in the next 12 months.

So not only we've now demonstrated that there's this association with lung function, but there's also an association with future risk of asthma exacerbations. And therefore, this appears to be an adequate surrogate marker for future risk.

So in conclusion, in this part of the presentation, I'd like to summarize that we've now identified in terms of targeted therapy a subset of patients with this eosinophilic phenotype, which I believe the eosinophil is a key player in terms of driving the pathology.

We also have identified that we have an adequate surrogate biomarker. The circulating eosinophil level as measured by CBC with differential is something that is clearly available for clinicians to use, and that it's highly specific for the identification of airway eosinophilia, and that it's associated with substantial morbidity in our patients, lower lung

function and future asthma exacerbations.

Therefore, we really need an ideal therapy, as we'll talk about subsequently, that's going to target this phenotype of patients with uncontrolled asthma that have this eosinophilic phenotype in order to reduce their current impairment, improve their symptoms and their future risk.

Certainly, as we learn more and more about these patients, what's driving their pathophysiology, we've identified that this is a unique endotype that we can use to treat our patients and reduce their subsequent impairment and risk.

I'd now like to turn it over to Dr. James Zangrilli to talk about the clinical efficacy of reslizumab.

Sponsor Presentation - James Zangrilli

DR. ZANGRILLI: Thank you. James Zangrilli, clinical lead for reslizumab. Today I'm going to focus on three areas, including dose selection of blood eosinophil inclusion, the key phase 3 efficacy results in asthma patients with elevated

blood eosinophils, and finally the efficacy results for select subpopulations. First, let's revisit the high-level program that Dr. Shah described.

Reslizumab dose selection was based on early studies in asthma patients with and without evidence of eosinophilic inflammation. Additional dose justification is provided as part of the phase 3 program.

Both studies 350 and 290 tested reslizumab at doses of up to 1 milligram per kilogram in unselected asthma patients. Three milligrams per kilogram was subsequently tested in targeted patients with either elevated sputum eosinophils, study 10, or elevated blood eosinophils, study 3081. Study 3081 also included a lower 0.3 milligram per kilogram dose level.

A blood eosinophil threshold of 400 cells per microliter was suggested for phase 3 based on published data suggesting that this level would be specific for airway eosinophilia. All comer study 3084 was designed to look at efficacy in patients both with and without elevated blood eosinophils.

Finally, two 52-week exacerbation studies, studies 3082 and 3083, provide replicate asthma exacerbation data.

Let me take you through the results. Early studies in unselected asthma patients met proof of principle for blood eosinophil lowering, particularly for doses greater than or equal to 0.3 milligrams per kilogram. However, no clinical improvements were observed at the highest dose tested, 1 milligram per kilogram.

As Dr. Shah pointed out, reslizumab development in asthma paused at this point but was subsequently picked up with study 10. Study 10 focused on patients with sputum eosinophilia. To help ensure the success of this study, a dose of 3 milligrams per kilogram was selected for further testing. The theory was that higher doses may be needed to treat tissue eosinophilia. A 4-week dosing regimen was chosen for this study, consistent with the established half-life of reslizumab.

Study 10 enrolled adult patients with sputum

eosinophils of at least 3 percent. They had to be uncontrolled on medium to high doses of inhaled corticosteroid, or ICS, with or without another asthma controller. Patients were randomized to 4 monthly doses of reslizumab at 3 milligrams per kilogram or to placebo.

Primary efficacy was based on the change in Asthma Control Questionnaire 7 score, or ACQ for short. ACQ is a patient-reported measure of overall asthma control but also considers rescue inhaler use and airway caliber.

Phase 2 study 10 was the first robust demonstration that reslizumab could benefit patients who are selected for the presence of active eosinophilic airway inflammation. The reslizumab group is represented by the blue line. We saw improvement in ACQ score over time where a negative change in ACQ indicates improving asthma control. Lung function based on FEV1 was also improved in this study.

These improvements in asthma control were accompanied by a decrease in the percentage of

sputum eosinophils at the end of treatment as depicted by the blue bars.

An elevated blood eosinophil count was chosen as a practical surrogate of airway eosinophilia for the phase 3 studies. As discussed by Dr. Castro, blood eosinophil counts of at least 400 cells per microliter should predict airway eosinophilia with high specificity. This relatively high threshold was intended to help exclude patients without the disease state and who would be less likely to benefit from add-on reslizumab.

To help inform these questions, two parallel 16-week lung function studies in asthma patients were conducted. Study 3081 included targeted patients with blood eosinophil levels greater than or equal to 400, and study 3084 allowed any blood eosinophil level.

Study 3084 was conducted to help understand efficacy in patients unselected by baseline blood eosinophil counts. Adult patients with uncontrolled asthma were enrolled. Approximately

80 percent of the patients had a baseline blood eosinophil count of less than 400.

Patients were randomized to 4 monthly doses of reslizumab or to placebo. Primary efficacy was based on change in FEV1 at 16 weeks.

This graphic represents the change in FEV1 by treatment for the unselected asthma population. As you can see by the blue line, a modest and nonsignificant treatment effect was observed.

This graphic demonstrates the treatment effect by different baseline blood eosinophil thresholds shown on the X-axis. The bars represent the treatment difference relative to placebo on the Y-axis.

The light blue bars represent the treatment difference for all patients with eosinophil counts below the specified cutoff. The dark blue bars show this difference above the cutoff. For example, the light blue bar shows the treatment difference for all patients with a baseline blood eosinophil count below 300. The dark blue bar shows the treatment difference for all patients

with a baseline eosinophil count of 300 and above.

Looking at the light blue bars, blood eosinophil cutoffs less than 400 did not select for reslizumab responsive patients as assessed by either FEV1 or by ACQ score. In contrast, changes in these measures were more substantial for the subset of patients with a baseline blood eosinophil count greater than 400 represented by the dark blue bar to the far right.

We understand that there is interest in discrete eosinophil categories below 400. To help inform this, the FEV1 was stratified by eosinophil quartiles as a post hoc exercise. This analysis was not included in our briefing materials.

Here we see no effect at very low eosinophil counts with positive changes in FEV1 observed only for the upper quartiles. This result supports the eosinophilic phenotype is essential to reslizumab efficacy.

We previously established that reslizumab markedly reduces sputum eosinophils. In the next few slides, I'll present additional supportive data

for this dose level, including the results from study 3081, which tested a lower 0.3 milligram per kilogram dose. I will also describe the response to intermediate doses of reslizumab based on PK/PD modeling of pooled study data in patients with elevated eosinophils. More detailed information is provided in your briefing package.

The design of study 3081 was the same as study 3084 except that patients had to have had blood eosinophil counts of at least 400 and adolescents were included. In addition, a lower 0.3 milligram per kilogram dose was also tested. Primary efficacy was based on change in FEV1 over the 16-week treatment period.

In study 3081, both doses significantly improved FEV1. The magnitude of the change was largest for the 3 milligram per kilogram dose arm at 160 mLs.

We also looked at other lung function, including forced vital capacity or FVC as shown here. A reduced FVC can be a marker of air trapping and obstructive lung disease. The

3 milligram per kilogram dose produced a substantial 130 mL improvement versus 0.3 milligram per kilogram dose produced no meaningful effect.

This result suggests that higher doses may be necessary to adequately treat the airway where asthma pathology predominantly resides.

We also observed a dose dependent decrease in blood eosinophils in this study. Here the 3 milligram per kilogram dose level produced the largest decrease in blood eosinophils as shown by the blue line at the bottom. The 0.3 milligram per kilogram dose represented by the orange line in the middle produced a smaller decrease. Placebo shown by the gray line on the top produced no meaningful change.

Finally, both doses produced improvements in Asthma Quality of Life Questionnaire, or ACLQ, and ACQ score. In both cases, the magnitude of the treatment effect was largest for the 3 milligram per kilogram dose. Asthma Symptom Utility Index, or ASUI, assesses the frequency and severity of asthma symptoms. This measure as well as short-

acting beta agonist use demonstrated similar degrees of improvement at both dose levels.

In order to further understand the effective dose, blood eosinophil and efficacy responses were modeled against different doses of reslizumab. The analysis utilized pooled clinical trial data from approximately 900 patients who met a cutoff for elevated blood or sputum eosinophils.

A Q4-week dosing regimen was assumed. In this graphic, the red saw-toothed line represents the 0.3 milligram per kilogram dose level, the blue line represents 1 milligram per kilogram, and the green line at the bottom represents 3 milligrams per kilogram. The black line across the top represents the placebo response.

The results indicate that the 3 milligram per kilogram dose is predicted to produce maximum blood eosinophil suppression with the least fluctuation between doses. Likewise, modeling of the FEV1 and ACQ responses by dose predicts larger improvements as the dose increases through 3 milligrams per kilogram. In this pooled analysis,

the 0.3 milligram per kilogram dose, produced small changes in these measures.

In summary, study 10 demonstrated that reslizumab 3 milligrams per kilogram reduced sputum eosinophils by 82 percent, which was associated with clinical benefits. In addition, study 3081 showed that this dose produced larger reductions in blood eosinophils and greater improvements in measures of asthma impairment than a 0.3 milligram per kilogram dose.

Finally, PK/PD modeling predicted larger treatment effects for the 3 milligram per kilogram dose versus lower doses.

I'd now like to move to the replicate 52-week trial results for studies 3082 and 3083. The key inclusion criteria for these studies were the same as for study 3081 except that patients were required to have had at least one asthma exacerbation requiring the use of systemic corticosteroid during the previous 12 months. Maintenance use of oral corticosteroid was also permitted in these studies.

The primary efficacy analysis for these studies was the frequency of clinical asthma exacerbations, or CAEs, over the 52-week treatment period. Key secondary efficacy measures were tested in a hierarchical fashion and included FEV1, AQLQ, ACQ 7, the time to first asthma exacerbation, Asthma Symptom Utility Index, or ASUI, relief bronchodilator use, and blood eosinophil count.

I've indicated the scales for these measures and the minimal clinically important treatment differences where relevant.

For these studies, a clinical asthma exacerbation was defined as a worsening of asthma that required a medical intervention that was above and beyond the patient's usual care. The definition accommodated medical interventions, including new or increased use of systemic corticosteroid, increased use of inhaled corticosteroid, other emergency treatments for asthma, emergency room visits, or hospitalization.

Worsening of asthma was based on worsening asthma symptoms or on a decrease in lung function.

All events were adjudicated by a committee of three independent, blinded asthma experts who ultimately decided whether an event met the current protocol definition or not.

The demography of the study populations are shown here. Patients were predominantly adult and of white race. The percentage of black patients was small. The increased proportion of females to males is consistent with the asthma disease state. The majority of our patients were ex-U.S.

This table highlights selected baseline disease state characteristics for both studies. These studies were well balanced between the treatments arms within and across the studies. The average number of historical asthma exacerbations for this population was two. The average screening ACQ score was greater than 1.5, and lung function was lower than normal. Overall, these characteristics are consistent with an uncontrolled asthma population.

Patients were required to maintain their usual controller regimen throughout the treatment

period. Slightly more than 40 percent of the patients were on high doses of ICS at baseline. The vast majority of patients were using an additional asthma controller.

Approximately 80 percent of patients were using a long-acting bronchodilator. A subset of patients were using OCS.

I will now turn to the efficacy results for these trials. Exacerbation reductions are represented in this graphic as rate ratios. The ratios represent the exacerbation rate for reslizumab relative to placebo over the 52-week treatment period.

Here and for subsequent graphics, study 3082 is represented by the blue bar and study 3083 by the green bars. For ease of review, effects favoring reslizumab are shown in the portion of the graphic shaded in yellow.

Primary efficacy was met for both trials with 50 percent and 59 percent reductions in the overall asthma exacerbation rate for studies 3082 and 3083, respectively. The majority of patients

with at least one asthma exacerbation required the use of systemic corticosteroid. The result of a prespecified sub-analysis for this type of event was consistent with the primary analysis.

Exacerbations requiring a hospitalization or an ER visit or hospitalization alone were rare. Therefore, the study results were integrated as shown here by the black bars. A trend for reduced hospitalizations and ER visits was observed.

In addition to the reduction in the annual rate of asthma exacerbations, reslizumab significantly increased the time to first exacerbation event. Here the probability of not having an asthma attack is plotted over time with reslizumab depicted by the blue bars.

As Dr. Castro discussed, improvement in measures of current asthma control is an important treatment goal. Reslizumab consistently improved multiple measures of current asthma control. Improvements in lung function based on FEV1 is shown here over 16 and 52 weeks.

In both studies, improvement in FEV1 was

observed after the first dose of reslizumab at the first 4-week assessment. These improvements in FEV1 were maintained through week 52.

Patient-reported outcomes were also significantly improved as shown on this slide for Asthma Control Questionnaire scores over 16 and 52 weeks.

Asthma Symptom Utility Index scores, shown on this slide, were also improved over 16 and 52 weeks. Asthma Quality of Life scores were first assessed at week 16 and then periodically through week 52. As you can see here, change in asthma-related quality of life scores also favored reslizumab.

Asthma Control and Asthma Quality of Life measures have established thresholds relating to a minimal clinically important treatment difference or MCID. In these analyses, the frequency of ACQ and AQLQ responders based on the MCID was larger for reslizumab than for placebo at week 52.

In summary, we studied asthma patients with elevated blood eosinophils who were inadequately

controlled despite the use of medium to high doses of ICS. The majority of these patients were also using a LABA. Both studies met primary and most key secondary efficacy endpoints. These included a significant reduction in the annual rate of asthma exacerbations as well as significant improvements in lung function and patient-reported measures of Asthma Control and Quality of Life.

The primary efficacy results continue to be strongly positive following sensitivity analyses for missing data and for protocol violations. The results of these analyses are included in your briefing materials.

Finally, we looked at the potential influence of certain intrinsic and extrinsic factors on reslizumab efficacy. These included type of background medication used and patient demography. Analyses were based on the reduction in clinical asthma exacerbation rate and the change in FEV1. The blood eosinophil pharmacodynamic was also analyzed for demographic subgroups.

Understanding that these trials were not

designed or powered to test efficacy in smaller subpopulations, data were pooled across the three studies.

This graphic shows exacerbation rate ratios on the left and change in FEV1 on the right by major classes of background asthma medication used. Please recall that all patients had to be on a background of at least medium dose ICS. In this analysis, other controller medications used were not mutually exclusive.

The result for the overall pooled 3082 and 3083 population is shown at the top, followed by oral corticosteroid use, ICS LABA categories, ICS without LABA, and leukotriene inhibitors. These results indicate that reslizumab produces reductions in the rate of asthma exacerbation and improvements in FEV1 irrespective of the type of background controller medication used.

The influence of demography is evaluated in the next three slides. This slide depicts reslizumab effect by age where treatment effects were observed for most analyses where reslizumab

did not reduce the asthma exacerbation rate ratio in the adolescent subgroup, which contained only 25 patients. However, changes in FEV1 and blood eosinophils favored reslizumab.

We understand that an exacerbation rate ratio that favors placebo appears to suggest that reslizumab confers an increased risk of asthma exacerbation. This table shows the number of baseline historical asthma exacerbations for the overall population and for adolescent patients. These historical averages are contrasted with the observed exacerbation rates during the treatment period.

There was a substantial imbalance in the exacerbation risk for the reslizumab group at baseline at approximately three per year as shown in yellow. This was not improved by treatment with reslizumab.

On an individual study basis, this imbalance was driven by study 3082 where the reslizumab group had an unusually high historical and treatment period exacerbation rate. This is shown by the

yellow shading. This is one example of how analyses and smaller subgroups may yield anomalous results.

Reslizumab effect by race is shown here where treatment effect favoring reslizumab was seen for most analyses. Reslizumab did not reduce the exacerbation rate ratio in the black subgroup, which consisted of 44 randomized patients. However, the effect on FEV1 improvement and on eosinophil reduction was similar to that seen for the overall population.

Finally, the effect of reslizumab by region was examined where effects were observed for most analyses. Reslizumab did not reduce asthma exacerbation rate ratio for the U.S. population. However, changes in FEV1 improvement and eosinophil reduction were similar to that observed for the overall population.

While these trials were not designed to test efficacy in specific subpopulations, subgroup analyses showed the reslizumab reduced asthma exacerbations on top of a broad range of asthma

therapies and for most demographic subgroups. The apparent lack of effect on exacerbation rates for certain demographic groups may be related to anomalies produced by the analysis of rare events in smaller unbalanced subgroups.

In fact, reslizumab produced the expected directional changes in physiological measures of lung function and blood eosinophil count in all three subgroups consistent with the overall population.

These observations plus the substantial efficacy observed for the overall randomized population indicate that the exacerbation results for adolescents, blacks, and the U.S. subpopulations are due to chance.

As Dr. Castro discussed, the goal of asthma therapy include improving current asthma impairment and reducing future risk, particularly the risk of asthma exacerbations. Reslizumab 3 milligrams per kilogram was highly efficacious in uncontrolled exacerbation-prone asthma patients with elevated eosinophils, the majority of whom are using medium

to high doses of an ICS LABA preparation.

In this population, consistent improvements across multiple measures of asthma control were observed, including meaningful reductions in asthma exacerbations and significant improvements in lung function, asthma symptoms, and asthma-related quality of life.

My colleague Dr. Yael Shalit will now discuss the safety profile of reslizumab.

Sponsor Presentation - Yael Shalit

DR. SHALIT: Thank you. Today, I'll review reslizumab's extensive safety database as well as its overall adverse event profile, including both long-term use and safety in adults and pediatrics. I'll then review AEs of special interest and conclude with an overall safety summary.

The data I will present comes from large global clinical development program with nearly 2200 subjects exposed to reslizumab in 14 clinical studies, 13 of them sponsored by the company. The program used various indications and doses. Most of the data comes from asthma studies, which used

the dose of 3 milligrams per kilogram every 4 weeks.

These studies were used to build the primary integrated safety analysis. They included five placebo-controlled asthma studies and one single open label extension studies in patients that were treated for up to an additional two years.

Of note, two studies were conducted in pediatric patients where there was eosinophilic esophagitis. The data from these studies supported the evaluation of the safety in the adolescent population.

Finally, the integrated analysis of all subjects exposed to reslizumab was used to evaluate any potential rare events.

The study generated nearly 2200 patient years of exposure. In the placebo-controlled and open label extension studies, almost 750 asthma patients were treated with 3 milligrams per kilograms for more than a year while over 200 were treated for more than two years. In the overall program, more than 60 patients were exposed to at

least three years of treatment.

Let's now look at the demographics of the asthma studies. These studies were conducted in 31 countries. As a result, the demographics reflect a global population and are comparable across treatment groups.

A total of nearly 750 patients were from the United States. Note that there were slightly more U.S. patients in the reslizumab group. That's because one study, 3084, was conducted only in the U.S. It had a randomization ratio of 1 to 4 placebo versus reslizumab.

Overall in the placebo-controlled asthma studies, the incidence of adverse events was similar or lower in the reslizumab group compared to placebo. In fact, AEs were high in the placebo group by nearly 15 percent. Likewise, serious adverse events were reported at a higher rate in the placebo group. AEs that led to discontinuation were similar across groups.

Reslizumab was tested in different doses in early stage studies as well as in one phase 3

study, study 3081. Approximately 500 subjects were exposed to doses less than 3 milligrams per kilogram. The review of the safety data of these individual studies showed similar safety profile of doses less than 3 milligrams versus the 3 milligram dose, and no dose-related adverse effects were seen.

Common adverse events were defined as those reported by at least 2 percent of the patients, regardless of causality. Like the overall AEs, most occurred in higher incidence in the placebo group. Of those events reported at a higher rate in the reslizumab group, the difference was always less than 1 percent compared to placebo. This applies to both common and overall adverse events.

The incidence of the overall serious adverse events was relatively low and generally similar across treatment groups. Mostly, they were single events. Here we see the serious adverse events that occurred in more than one patient. The most common events in both treatment groups were asthma and pneumonia.

Falls, chest pains, and anaphylactic reactions were reported only in the reslizumab group. All cases of chest pains were judged to be of non-cardiac origin, were not temporally linked to the infusion, and were evaluated by the investigators as unrelated to reslizumab.

Moreover, the overall incidence of all cases of falls and chest pain, including both serious and non-serious events, was comparable across treatment groups.

Three of the four serious anaphylaxis cases were assessed as drug related by both investigator and Teva. The fourth case was associated with a known walnut allergy. I'll discuss these cases later in the presentation.

For AEs that led to discontinuation, here we see that both the incidence and nature were similar across treatment groups with the exception of the three anaphylaxis cases reported on reslizumab.

There were 4 deaths in the entire program, one in a placebo-treated patient and three in the open label extension study. None of the deaths

were assessed as related to treatment, and none were due to uncontrolled asthma.

Let's now turn to the long-term safety. Over 750 asthma patients were treated with reslizumab 3 milligram for more than a year. The AE profile of this subset of patient was similar in both treatment groups. Moreover, when we look at AEs by time of occurrence, as seen in this chart, we do not see an increase of AEs over time.

Specifically, we also do not see an increase in the events of special interest such as infections show in gold, malignancies shown in green, or myalgia shown in pink. Finally, no anaphylactic reactions were reported after 12 months of treatment.

Let's turn our attention to the pediatric patients. The program included more than 250 pediatric patients treated with reslizumab. Thirty-eight of these patients were asthma patients between the ages of 11 to 17. More than 200 others were eosinophilic esophagitis patients between the ages of 5 to 18. Most of these patients were

treated for more than two years.

Nearly a third of those eosinophilic esophagitis patients, however, were treated for more than three years. It's worth noting that about 50 percent of those eosinophilic esophagitis patients were adolescents and about half of them had asthma.

As summarized in the lower table, the overall pediatric AE profile was similar to placebo and similar to the AE profile of the overall population.

In looking at other safety measures except for the pharmacological effect of reducing eosinophils, we saw no evidence of treatment effect on clinical laboratory measures. Additionally, we saw no effect on electrocardiograms and vital signs.

Reslizumab is a biologic therapy. It is administered via intravenous infusion and has a mechanism of action leading to eosinophil suppression. Given those realities, the evaluation of systemic hypersensitivity reactions,

immunogenicity, infections, and malignancies were of special interest in the evaluation of its safety profile.

Moreover, given the slight imbalance of myalgia cases in the integrated safety analysis, we also looked on muscle AEs and creatine phosphokinase levels, which I'll present shortly. Now, however, let's turn to the important issue of anaphylaxis.

In the entire clinical program, there were 12 patients who experienced anaphylactic reactions as reported by the investigators. Of these, 11 were reslizumab-treated patients. One was a placebo-treated patient.

Nine of these cases were associated with exposure to food allergens or allergy shots. Three of the cases were temporally linked to reslizumab infusion and were assessed as related to the infusion. These cases resulted in treatment discontinuation.

Let's look in more detail at these cases, beginning with the nine cases not related to

reslizumab exposure. Seven of the nine cases occurred in the pediatric eosinophilic esophagitis studies. Three of those cases occurred in the placebo-controlled study, two on drug, one on placebo. The other four cases occurred in the open label extension study. The remaining two cases occurred in the placebo-controlled asthma studies in patients treated with reslizumab.

In all of the nine cases, anaphylaxis was temporally linked to ingestions of known food allergen or administration of allergy shots. None of these events were temporally linked to reslizumab infusion, and importantly, none resulted in reslizumab discontinuation.

Of note, one patient with a known wheat allergy from the esophagitis study did not continue treatment after experiencing anaphylaxis to wheat because of lack of effect.

Let's take a more detailed look at the remaining three cases, those related to reslizumab infusion. All three cases occurred in the phase 3 asthma studies. The reactions occurred within

20 minutes after the second or 12th infusions. There were no delayed symptoms. All patients were on site when the event began. Reactions consisted of skin or mucosal involvement, dyspnea or wheezing, gastrointestinal symptoms and chills. None involved circulatory collapse or respiratory failure.

All cases fully resolved within a few hours after treatment, and patients were discharged to home. All cases resulted in discontinuation of treatment.

These three patients were atopic. Two also had a history of drug hypersensitivity and prior anaphylactoid reactions to aspirin. Of note, diagnosis was made by the site investigator based on clinical judgment, and no confirmatory tests were performed.

Finally, all patients had undetectable alpha-gal IgE with no prior history of tick bites or meat allergy.

Given these events, we performed additional searches in order to detect possible unrecognized

systemic hypersensitivity and infusion reactions. This included a review of the standard MedDRA queries, or SMQs, involving anaphylactic reaction and angioedema. These SMQs are a valid grouping of common terms that could be associated with anaphylaxis or angioedema.

The incidence was higher in the placebo group for anaphylactic reactions SMQ both in the overall and on day of or day after the infusion as well as for angioedema. We also reviewed specific reports of hypersensitivity and infusion-related reactions.

As you can see here, the incidence of these cases was similar to placebo. Moreover, they were all associated with other allergens except for one case. This case, however, like all other cases, continued treatment with reslizumab with no reactions.

Finally, as part of the thorough evaluation to detect possible unrecognized anaphylactic reactions, we performed the following: The 439 events falling under the broad search of

anaphylactic reactions that occurred on the day of or the day after the infusion in both placebo and reslizumab asthma patients were all narrated and reviewed by an external, independent and blinded adjudication committee.

In the table are the event terms of the cases that were reviewed by the committee. As you can see, the majority of events were derived from asthma reports that were higher in placebo. All other events were similar in both treatment groups with the exception of the three reported anaphylaxis reactions.

Let me take a moment to describe the committee, the process, and their findings. The external committee consists of five external non-Teva physicians trained in allergy who were familiar with the diagnosis of anaphylaxis. They followed a predefined adjudication process.

Each case was blinded and adjudicated against Sampson criteria number 1, which establishes clinical criteria to identify cases of anaphylaxis. The Sampson criteria is shown on this

slide. Each case narrative was reviewed by at least two physicians and adjudicated as highly likely or not highly likely an anaphylactic reaction. Now, let's look at their findings.

A total of four cases of anaphylaxis were identified by the adjudicators, three in the reslizumab arm and one in the placebo arm. I'd like to remind you the original reports of anaphylaxis reported by the site investigators. As you recall, the site investigators reported three cases on reslizumab and none on placebo. These are shown here.

The action taken with study medication for each of these cases is shown in the final column. Let's walk through each case row by row to gain a full understanding of each of them.

The first two cases in the reslizumab arm were reported by both the committee and the investigators. Both cases resulted in discontinuation. The third and fourth cases were identified only by the committee, one on reslizumab and one on placebo. The patient on reslizumab,

however, continued to receive 13 additional infusions with no adverse reactions related to those infusions.

Finally, the fifth case shown in the table was reported as anaphylaxis by the site investigator but was not adjudicated as such. This patient discontinued treatment.

Narrative for each of these cases have been provided in your briefing materials. Given all this, Teva believes that the most clinical, relevant and potentially drug-related anaphylaxis cases were the three cases reported by the site investigators.

The adjudication process was a very thorough search for potential additional cases. We are reassured that although the adjudication panel findings were slightly different, this process did not dramatically change our appreciation of the overall anaphylaxis risk.

In summary, uncommon anaphylactic reactions are designated as an adverse drug reaction and are recognized risk for biologics. Anaphylactic

reactions are considered manageable, taking into account both the setting of administration by a healthcare professional prepared to manage anaphylaxis and the lack of evidence of delayed onset or protracted progression. And finally, anaphylactic reactions are important events, and both patients and prescribers will be made aware of this risk by way of appropriate labeling.

Let's turn now to the issue of immunogenicity. Immunogenicity was of low incidence with no observed clinical impact. Immunogenicity was evaluated in the phase 3 program in over 1,000 asthma patients treated with reslizumab for up to three years. The immunogenicity assay, which is able to capture all antidrug antibody isoforms, has a sensitive of 22 nanograms per milliliter, which exceeds the FDA recommendations.

Approximately 5 percent of reslizumab-treated patients developed antidrug antibodies, ADA. The ADA titers of these patients were low, and their presence was frequently transient. There

were no indications that the presence of ADA affects the exposure to reslizumab. Additionally, eosinophil counts as well as the safety and efficacy profile in the patients who had ADA response were similar to the patients who had no ADA response. And finally, there were no reports suggesting hypersensitivity in patients with ADA.

Next, under the topics of events of special interest, we will discuss infections. The overall incidence of infections was high in the placebo group. Commonly reported infections were those of respiratory tract as expected in asthma population. Also, the serious infection events were similar to placebo in both incidence and type. And finally, there was no evidence of a risk for opportunistic or atypical infections.

Based on the mechanism of action of reslizumab, a theoretical risk exists that lowering the eosinophil levels will affect the immune response to parasitic helminth infections. Our global clinical studies included nearly 400 patients from countries known to be endemic for

helminth infections. More than half of these patients were treated with reslizumab; yet, there were no reports of helminth infections.

Moreover, the review of AEs that might be associated with these infections such as anemia, elevations of liver function tests, and gastrointestinal symptoms, did not suggest a difference between placebo and reslizumab.

Turning to malignancies, there was no suggestive causality between reslizumab treatment and the increased risk of malignancies. In the nonclinical studies with reslizumab, including the mouse carcinogenicity study, there were no mutagenic or carcinogenic findings as detailed in the briefing materials.

In the placebo-controlled asthma studies, there was an American balance in reported malignancies, 6 patients in the reslizumab group as compared with 2 patients in the placebo group. In the open label extension study in which patients were treated up to an additional two years, 15 patients were diagnosed with malignancies.

Except for the malignancies diagnosed in the phase 3 studies, there were no additional malignancies in the reslizumab-treated patients. If we look closer to the reports of malignancies, patients with previous malignancies were not excluded from the clinical studies, and in two patients, the malignancy reported was a reoccurrence.

Additionally, the malignancies that were diagnosed were of diverse origin and tissue types, suggesting no common mechanism of carcinogenicity. The most common reported malignancies were non-melanoma skin cancer.

Except for one skin squamous cell carcinoma, all malignancies in the placebo-controlled studies were diagnosed with less than six months after initiating reslizumab treatment. This short latent period suggests that these were preexisting conditions.

Finally, as presented in the briefing document, the malignancy rate for both placebo and reslizumab arms generally had reporting rates

similar to the published rates in the SEER database. To summarize, the evaluation of cases did not support an association between reslizumab and malignancies.

In looking at the final safety topic, our review of the integrated safety data revealed a slightly higher incidence of myalgia in the reslizumab group, 10 cases on drug versus 4 in placebo. Moreover, CPK elevations greater than five times the upper limit of normal were more prevalent in the reslizumab group. Of note, this signal was not seen in early stage studies.

Teva conducted a thorough evaluation to better understand whether muscle adverse events and CPK abnormalities could be related to drug exposure and indicative of myositis or rhabdomyolysis. These evaluations and findings are fully described in the briefing materials and included the following.

The review of the baseline characteristics showed that patients treated with reslizumab had more ongoing musculoskeletal manifestation at

baseline and used more medications that are commonly used to treat these complaints. Additionally, the use of statins was also higher in patients in the reslizumab group.

Moreover, there were more patients in the reslizumab group with elevated CPK at baseline, 14 percent in reslizumab versus 9 percent in placebo. This was also reflected in higher values of baseline mean and median CPK in the reslizumab group.

The CPK elevations reported during the treatment period were mostly low grade, transient, and in most cases, not associated with muscle complaints. None were serious events. Importantly, blood sampling was done on the day of the infusion before the infusion. Thus, the temporality of CPK elevations and drug administration is limited.

In view of the imbalance in baseline CPK values, we also analyzed CPK elevation during the study in patients with normal CPK values at baseline, as shown in this slide. The shifts to

elevated CPK levels were slightly higher in the placebo group in the grades 1 and 3, while shifts in grades 2 and 4 were slightly higher in the reslizumab group. Overall, there was no trend for reslizumab effect on CPK values.

Additionally, the PK/PD analysis that were conducted did not show an exposure response relationship with CPK values.

We also narrated and reviewed cases that involved musculoskeletal AEs and/or significant elevated CPK values. These cases are summarized in this slide and included the following: all events under the system organ class of musculoskeletal disorders and AEs of elevated CPK that were reported as either serious events or led to discontinuation, as well as musculoskeletal events that started on the day of the infusion. We also reviewed events falling within the broad list of terms that may be associated with myopathy.

Finally, we reviewed all cases with significant elevated CPK levels. As summarized in the table, the incidence of this event was similar

in both treatment groups. Of note, all CPK elevations greater than 10 times the upper limit of normal were asymptomatic. Moreover, as detailed in the briefing document, the review of these cases did not detect any events consistent with myositis or rhabdomyolysis.

So to conclude, we thoroughly investigated the possible muscle safety signal as presented in our briefing document and in the last few slides. Uncommon transient, non-serious or severe myalgia is a signal for reslizumab, although it might have been due to a chance. Importantly, there is no evidence that reslizumab is associated with muscle injury.

So to summarize, the reslizumab safety profile is well characterized and overall favorable. Our global development program included long-term use, up to three years of treatment, as well as over 250 children and adolescents across all trials. There is no evidence of immunosuppression. Immunogenicity is low and not linked to adversity or lack of effect.

Treatment was associated with uncommon anaphylactic reactions. However, this important event is manageable in the setting of IV infusion given by a healthcare professional prepared to manage anaphylaxis. Importantly, there were no delayed or protracted reactions, and all cases resolved following standard treatment protocols.

Uncommon myalgia was reported at slightly higher incidence in reslizumab-treated patients with no association with CPK elevation or muscle toxicity. Otherwise, the overall safety profile of reslizumab is similar to placebo.

Taken together, these observations support our conclusion that reslizumab has a favorable safety profile. Thank you.

I will turn over the floor to Dr. Castro, who will present the clinician's perspective.

Sponsor Presentation - Mario Castro

DR. CASTRO: Good morning again. I'd just like to summarize again from a clinician's perspective how I see this data for my patients and how I see this drug potentially being used in

clinical practice.

Now, as we started, we talked about this unmet need and the importance of having adequate therapy and effective therapy that's safe for this small proportion of patients. And as Dr. Shah presented at the very beginning, this likely represents about 3 to 4 percent of the overall asthma population that would be an ideal candidate for an anti-IL-5 biologic therapy.

The data that was presented by Dr. Zangrilli demonstrates compelling efficacy data that shows that this drug works like we expect it to work. It reduces blood eosinophils, and the earlier study also showed the effect on sputum eosinophils.

The efficacy data that we demonstrate shows that this reduces current impairment when patients are treated with reslizumab in comparison to placebo, and this is associated with improvement in symptoms, improvement in quality of life, and improvement in FEV1. But also, it reduces future risk in that it reduces exacerbations, and these exacerbations reduction is quite substantial, about

50 to 60 percent, which is not something we see with our typical therapy in these patients right now.

So when one takes this into consideration, one has to again look at the data that Dr. Shalit presented in terms of the safety profile. And I believe that this risk of anaphylaxis, 0.14 percent, is definitely manageable in the scenarios where this drug will be administered, which is an IV therapy.

I believe that the physicians that will be prescribing this will have adequate expertise to treat any potential cases of anaphylaxis, as this will be used typically in pulmonary and allergy practices.

I'd like to go back to the patient, and I think this is important because when we consider the data in aggregate, sometimes we lose sight of the individual patient. So I'd like to share with you one of my own individual patients that participated in one of the pivotal studies.

This is a patient of mine in St. Louis who's

a 40-year-old African American male who had severe persistent asthma, really had been on high dose inhaled corticosteroids, fluticasone and salmeterol, and not been achieving control as demonstrated by his Asthma Control Questionnaire score of 2.0.

In addition, this patient not only wasn't achieving control, but he also had pretty high risk asthma in that he had multiple hospitalizations. In fact, one of these resulted in an ICU admission. Fortunately, he was not intubated, but was observed in our ICU.

His blood eosinophil count at baseline was 408. And fortunately, we were able to enter him in our clinical trial. He received treatment with reslizumab for over one year in study 3082, and much to my chagrin, my nurse coordinator said, "We need to participate in this open label extension because these patients are benefitting." She wasn't aware -- she was blinded, but definitely, patients were speaking to her.

So we participated in open label extension

in 3085 study. And this particular patient with the open label extension, he continued to demonstrate marked improvement in his asthma control with no exacerbations, no hospitalizations, and no adverse events.

It's demonstrated here by the key results, his Asthma Control Questionnaire score went from a 2 down to 1.1, which fits right in to kind of where we want our patients to be in terms of achieving asthma control. But also, improved his lung function significantly, about 180 mLs from baseline.

So demonstrating again that once we get back to these individual patients, once you identify this eosinophilic phenotype in our patients with inadequate control, that you're able to give them a targeted therapy with anti-IL-5 strategy with reslizumab to improve their overall control in a fashion, which we have not been able to do with previous therapy.

This also is nicely summarized with other patients that participated in the open label

extension study, and I'd just like to share some of those quotation marks because, again, I think from the patient perspective, we really need to take this into consideration.

The first patient, "It was like I didn't have asthma at all. I was symptom free for almost two years."

"I stopped wheezing and coughing, and once I was on the medication, I was only sick once. I could run on the medicine. I couldn't before. Before, I could hardly walk anywhere. Now on the medication, I could walk long distances."

I especially like this last quote especially for an IV therapy, "I looked forward to the monthly infusions because it made me feel awesome. There was a noticeable change in my asthma symptoms that I thought I would never experience."

So again, I think these are important patient perspectives to take into consideration as we consider the overall efficacy and safety of reslizumab.

Now, taking that into consideration, the

data that we've been presented this morning, I want to propose where I see this as a clinician fitting into our clinical practice here in the United States. These are the National Asthma Prevention Program guidelines, and as we know on the panel, this is a six-step therapy.

What we're looking for is really new therapies that we can use in our patients in step 4, 5 and 6 to improve their asthma control. And I believe that the data from the pivotal studies, from the phase 3 studies, demonstrate that there is this subset of patients that are in that step 4, 5 and 6 therapy that have an eosinophilic phenotype that is exacerbation prone and that is not achieving control with their current therapy with high dose inhaled steroids or moderate doses of inhaled steroids and a second controller agent.

I believe it's in this subset of patients that reslizumab really offers a profound benefit, and I truly believe that as a clinician, where you see a 50 to 60 percent reduction in exacerbations, including those requiring oral steroids, that's a

meaningful change for our patients in terms of reducing their asthma morbidity and with an adequate safety profile.

So I'd like to turn it over now to Dr. Shah for concluding remarks.

Sponsor Presentation - Tushar Shah

DR. SHAH: We realize that we have just presented a lot of information, and I would like to take a moment to summarize some of the key points. Reslizumab met its primary efficacy endpoint in all three pivotal clinical trials.

In patients who are exacerbation prone and inadequately controlled on medium to high dose ICS, corticosteroid-based regimen and have elevated blood eosinophils, reslizumab was shown to substantially reduce exacerbations and consistently improve lung function, symptoms, and asthma-related quality of life.

We have a well characterized and reassuring safety profile with approximately 1596 patients treated with a 3 milligram per kilogram dose with asthma. Of these, 743 were treated for more than

one year, and 213 were treated for more than two years. Additionally, we have safety data in approximately 250 children and adolescent patients, 64 of whom were treated for over three years, which also was very reassuring.

Shown in this slide is a graphical presentation of the benefit-risk profile of reslizumab based on the totality of the clinical program. A summary of the key efficacy data is shown on the top and safety data on the bottom.

For the efficacy results, data on exacerbations were pooled from studies 3082 and 83, and data on FEV1, AQLQ and ACQ were pooled from all three pivotal efficacy trials.

As reviewed by Dr. Zangrilli, reslizumab was shown to reduce exacerbations by more than 50 percent and consistently improve lung function, asthma-related quality of life, and asthma control.

The safety data is presented as percent difference in risk observed on reslizumab as compared to placebo. We also analyzed the data using odds ratio with similar conclusions. The

source of the safety data is all placebo-controlled asthma trials with the exception of anaphylaxis where it includes all studies where more than a single IV infusion was administered.

CPK elevation has been raised as an area of concern. Much of the differences that we observed in CPK elevations was due to baseline imbalances in the treatment groups. When we examined the data, when we correct for this with the baseline imbalance, we do not see any evidence that reslizumab treatment was assisted with CPK findings of concern.

When we looked at the clinical cases of musculoskeletal disorders as well as elevations in CPK, we did not find a relationship in that the patients who had CPK elevations did not have clinical complaints of concern of musculoskeletal symptoms. So based on that, we do conclude that the CPK elevations were driven by baseline imbalances and are not attributed to reslizumab therapy.

The only safety concern identified is a risk

of anaphylaxis, which was uncommon. This is not unexpected of a biologic agent and can be managed in the clinical setting as was seen during the trials.

Patient safety is very important to us, and we are committed to working closely with the FDA on appropriate labeling for healthcare professionals and patients around this risk.

This analysis supports that reslizumab has a favorable benefit to risk profile and addresses an unmet need in these difficult to treat asthma patients who have limited treatment options.

I would like to thank everyone for your attention, and we are now available for questions.

Clarifying Questions to Presenters

DR. OWNBY: Thank you very much. I'd like to thank the sponsor for staying within our time limits.

Are there any clarifying questions for Teva? Please state your name for the record before you speak. If you can, please direct your questions to a specific presenter.

Dr. Brittain.

DR. BRITTAIN: Yes. I have a couple questions on CE-16, if I have it right. So I guess you've made the point today there is comparison. You've made the point that you didn't see a statistically significant difference with the forced vital capacity with the low dose.

I'm wondering, was this particular study powered to see differences on this variable?

DR. SHAH: No. This was not designed or powered for this particular measure.

DR. BRITTAIN: Okay. And my second question relates to the safety analyses. This is something that I see all the time, so nothing unique to your presentation, but by lumping all the placebo patients and then all the drug patients together, you're creating a bit of an apples and oranges comparison because some of your trials had one-to-one allocations, and some of your trials that might have different entry criteria, have 3 to 1 drug to placebo. So it's a bit of a -- it's not quite an apples-to-apples comparison.

Is that something that you looked at, at all, or aware of, and made sure that when you were comparing, looking at your adverse events, that you were making sure that you were looking at like to like?

DR. SHAH: Absolutely. We also look at the rate because part of the issue is that exposure differences can exist, and that can drive clearly differences in incidence. And when we looked at the rates of exacerbation, our clinical adverse events adjusted for exposure, we don't see, again, any evidence of differences between the reslizumab and placebo groups.

DR. BRITTAIN: And you looked at that for the particular safety concerns that were -- I mean, not just overall adverse events. You looked at it at a deeper level?

DR. SHAH: Right. So obviously, anaphylaxis, we only had three cases that we felt were attributed to therapy, and it wouldn't make a difference how you analyzed that data.

DR. BRITTAIN: Right.

DR. SHAH: In the context of the CPK and the musculoskeletal, maybe Dr. Shalit can speak to the data on the rates.

DR. BRITTAIN: Yes, just again to mention, it isn't only just the difference in follow-up time. It is also difference in entry criteria. For example, the one study that had all comers had a different allocation than your other studies. So that's what I'm saying. It does create this little bit --

DR. SHAH: Sure.

DR. BRITTAIN: -- I don't tend to think that it's that critical in this particular situation, but I just wanted to mention it.

DR. SHAH: Sure thing.

DR. OWNBY: Dr. Tracy?

DR. TRACY: Jim Tracy. Can we pull up slide CE-27, please?

In this, I'm looking kind of at study 3082, and I noticed that under the oral corticosteroids, there's almost twice as many in the placebo group than in the treatment group. And that suggests to

me that we might be looking at two groups with different levels of severity.

I was wondering first of all, how would that happen, and second of all, do you believe that that may or may not affect efficacy issues or safety issues?

DR. SHAH: So in the context of the imbalance in that one study, we did have this issue with stratification errors in the trials. So this data is being presented as the way the patients' medication record acknowledged whether they were on oral corticosteroids or they were not.

Because when we did the trial, there were patients who had been captured as being on oral corticosteroids based on physician recording on the IVR system that they were on oral corticosteroids, and there were some errors made. And we explained that in the briefing document, that when we adjust for these errors, the effects of the treatment are unchanged.

So the short answer to the question is we did adjust for these differences in oral

corticosteroid, and the effect of reslizumab were robust regardless of whether you look at the patients not on oral corticosteroids as well as the ones who were on oral corticosteroids.

DR. TRACY: So in your opinion, these groups are comparable in terms of severity?

DR. SHAH: Yes. I mean, oral corticosteroid use is just one marker of severity, and that is a very small subset, as you can tell, of the overall patient population. Majority of the patients were not on oral corticosteroids, or approximately 90 percent of them were not on oral corticosteroids.

So these patients were quite comparable in terms of their severity between the two groups when you look at the totality of their other data that's up there.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: Thank you. I had two clarifying questions, and I hope that's okay. Could you bring up slide CE-40? This is one of the pediatric efficacy slides.

So if I'm understanding it correctly, the justification for why we're seeing the point estimate in the reverse favoring placebo for adolescents is due in part by the sponsor feeling that in 3082 that there was an imbalance in treatment between placebo and those on drug; is that correct?

DR. SHAH: That's correct.

DR. MORRATO: But despite that comparison, I'm seeing an increase in that trial among the reslizumab-treated patients going from 4 to almost 6. So that calls into question in my mind, the earlier assertion that eosinophils aren't necessarily a surrogate for future risk in this age group. So it's causing me to say, all right, is there other corroborating information? And I was wondering if you had two sources. One is can you present to us the findings for the ACQ and AQLQ results for the adolescents?

DR. SHAH: Maybe Dr. Zangrilli can answer that question.

DR. ZANGRILLI: We did look at ACQ, AQLQ,

and ASUI in these subgroups, and it didn't improve the result in the adolescents.

DR. MORRATO: So it's consistent with the lack of effect. Was that seen in both 3082 and 3083?

DR. ZANGRILLI: I'm sorry. The subgroup analyses are actually from the pooled 3082 and 3083. I don't have it broken down by study.

But in my view, as you pointed out, it appears even with this imbalance we're calling, it got a little worse with reslizumab treatment, I think is your point. But I think as far as your suggestion that eosinophils might not be important here, I think in this case, the eosinophils went down in these children, but obviously, they still exacerbated. So there's other factors that we just don't understand in this small subgroup.

DR. MORRATO: Very good. So the other source of data is the Price study, the large epidemiology population-based study that you cite earlier in your presentation. I did look up that study. It goes from ages 12 to 80. It was

sponsored by Teva.

Do you have results of what the association between eosinophil levels and the outcomes that were measured in that study for the 12- to 18-year-old population?

DR. SHAH: We don't have [inaudible -- off microphone.]

DR. OWNBY: Because this is being transcribed, we will wait for the microphone to be working.

DR. SHAH: Yes, much better. Sorry about that.

So the question is on the Price study, no, while that was a Teva-funded study, it was an independent trial done by Dr. David Price. We don't have the raw data in that particular analysis.

DR. MORRATO: It might be useful to get access to. I'm sure you could do an age subgroup.

The other question had to do with the anaphylactic management, and I understand the risk management is in the context of the kind of care

and the setting, which is important. But I also note that the case evaluation of the cause was not prospectively done, as you might expect in the trials. So what are the company's plans for the postmarketing pharmacovigilance, recognizing that given the background rate of anaphylaxis, trying to understand drug specific will be difficult based on spontaneous reporting alone?

DR. SHAH: So let me just kind of address that point since it is being raised by the FDA. We did not prospectively adjudicate anaphylaxis according to the Sampson criteria, but the physicians were respiratory physicians in the clinical programs. They were aware of the risk of anaphylaxis with biologic, as we made them aware of that concern and risk.

They were also aware and had to record adverse events as related to an infusion. So they were very sensitized that if there were infusion-specific adverse events, they needed to specifically inform us and identify those.

Finally, these patients were seen every

month. If they had a clinically meaningful anaphylaxis, we would have found it, and we would have had it reported. So I do think that while we didn't prospectively adjudicate anaphylaxis, it in no way suggests that we missed our anaphylaxis cases.

When we did a very thorough look at every event that could be considered anaphylaxis related, this kinds of symptoms that we see, worsening asthma, angioedema, urticaria, the typical things, we didn't see any differences or anything new. And that was reviewed by Dr. Shalit.

Additionally, we had an independent third party do it again at the FDA request, and they confirmed essentially that there was nothing major missed in terms of the anaphylaxis cases. So we feel that we have identified all the clinically relevant anaphylaxis cases in the program.

In the context of what we're committing to do afterwards, I mean, we will clearly work with the FDA and do whatever they believe is optimal to document that risk and manage that risk. But

again, we believe that this is a risk that physicians who are going to be administering biologic therapies like this understand that risk, and they are going to be able to deal with the consequences of that risk.

We are committed to have appropriate labeling, appropriate both for physicians and patients. We are also going to be providing information through the normal commercialization of a product, websites and such where these risks will be clearly identified and make patients aware.

Patients will be informed to be looking out for risks after the infusion in case they have a symptom or anything afterwards, and as we do today with our biologic therapies, to ensure that if they're having any problems, they immediately notify their physician so they can get the appropriate diagnosis and therapy.

We are committed to ensuring that it's done properly. It's no one's best interest for patients not to get a proper diagnosis and treatment of any of these issues.

DR. MORRATO: Thank you.

DR. OWNBY: I have six people on the list. Dr. Platts-Mills is next.

DR. PLATTS-MILLS: Thank you. I'd like to ask some questions about the molecule, and I wonder whether you could pull up figure 27 from page 84 of the briefing document. Is that possible? It's an elegant picture of the molecule --

Because the questions are -- this is an IgG-4 humanized molecule.

DR. SHAH: Correct.

DR. PLATTS-MILLS: And there are two possible modifications that could have been to it and which you don't mention. There are actually two disulfide bonds, and in IgG-4, the molecule often falls part. But I know that some companies -- so that if you look at reslizumab here, there's one disulfide bond marked, but in fact, there are two.

If the distance between the two disulfide bonds is changed, IgG-4 no longer falls apart. So the issue of whether the very small quantity of

alpha-gal on the Fc is relevant depends on how much the molecule falls apart. So I'd like to know that.

But also, is there actually a glycosylation site in the humanized part? Because there would normally be a glycosylation site up in the Fc of the heavy chain -- of the FAB section of the heavy chain, but that could have been engineered out. So there are two questions about it.

The third is that this is kappa, which is less usual than other monoclonals, and kappa is more immunogenic than lambda. So was there kappa specific immunogenicity of this molecule?

DR. SHAH: So let me have Dr. Jason Bock answer the question about the molecule specifically, and then we can talk about the immunogenicity question afterwards.

DR. BOCK: Jason Bock, CMC product development. So as you mentioned, IgG-4s can be hinge stabilized. This molecule did not have those mutations to modify the product. So there is a low level of the product that can disassociate. It's

in the mid-single digits. So that's the IgG-4.

Your second point was?

DR. PLATTS-MILLS: Whether there is actually a glycosylation site in the humanized section because I believe the mouse cell line could perfectly well glycosylate a humanized glycosylation site with some other oligosaccharide.

DR. BOCK: Good question. In the FAB portion of the molecule that was humanized, there was no glycosylation site that was removed, no glycosylation site.

DR. PLATTS-MILLS: So there wasn't a glycosylation site at all?

DR. BOCK: No.

DR. PLATTS-MILLS: There's another glycosylation site on the kappa, but you're not aware of that being glycosylated?

DR. BOCK: No. We've looked extensively at the glycosylation on the entire molecule and are confident that it is restricted to the Fc portion.

DR. OWNBY: Dr. Georas?

DR. SHAH: Did we want to answer the last

question about -- or are you comfortable that was addressed?

DR. PLATTS-MILLS: I think it's -- the kappa is not so common, and kappa is much more immunogenic than lambda.

DR. SHAH: So I think what for us is reassuring is when we looked at the immunogenicity, which would have measured any immunogenicity against any isoforms, we do not see any signal of concern in terms of the rate of immunogenicity. It's very consistent with what we would expect for humanized monoclonal antibodies.

DR. OWNBY: Dr. Georas.

DR. GEORAS: Thank you.

I have a general question and then a specific question. The general question -- and both of these relate to safety -- was, Dr. Shah, you mentioned you're committed to informing and managing anaphylaxis moving forward. I'm wondering if you could address in the development to date -- well, let me just make a comment first of all. In reading some of the case histories, I

thought it was strange that epinephrine was not used in many of those cases. It seemed like many of them would have risen to the level where epinephrine was indicated.

But could you address specifically the FDA perspective about not recording vital signs after infusion and why was that not a priority for the company? And then I have a second question after that.

DR. SHAH: So explaining why it wasn't in the phase 3, we had collected post-infusion vital signs in a large early -- all the earlier trials, and we saw no evidence of a concern with infusion of reslizumab in affecting vital signs. And that was done in several hundred patients of exposure over a long period of time.

So we felt that including that for every patient in the phase 3 program was unnecessary. Of course, in retrospect, maybe it would have helped, but I think clearly, it is something that from an anaphylaxis perspective, clinical presentation would be very difficult, I would think, if it was

meaningful anaphylaxis for us to miss those in the context of the way we administer the product.

The patients were there at the clinic during the infusion and after the infusion. It would have been very hard for me to imagine that if someone really had anaphylaxis, that it would have been missed in the clinical setting.

DR. GEORAS: Thank you. Then my second question is if you could bring up slide CS-27, and I guess this would be for Dr. Shalit.

As an eosinophil biologist, I have a nagging concern about anti-IL-5 or eosinophil-targeted therapies and tumor surveillance. And I'll have this concern for any compound in this class, and we discussed this a little bit in June. And the concern is not for immunogenicity per se but tumor surveillance.

So I appreciate the efforts made in the statements that this molecule was not mutagenic or carcinogenic. But as we move these compounds into the human population and look at years potentially of therapy, I personally am concerned about a

cancer risk. And I'll acknowledge upfront that the relationship between eosinophils and cancer is very complicated, very confusing with some studies suggesting pro-tumor effects of eosinophils, but an equal number, in my opinion, suggesting anti-tumor, including for colorectal cancer.

So the specific question then for you or Dr. Shalit is it seems to me there's a discrepancy between the data presented in this table and that presented in table 28 of the briefing document, specifically regarding the comparison to published malignancy rates. And in the presentation we just heard, I got the impression that there was no concern when doing this comparison using the SEER database.

But in the document we reviewed, table 28 in particular, it did look like even after making that comparison, there was a signal for higher than expected. So could you please just clarify that for me?

DR. SHAH: So maybe I'll have Dr. Shalit go over the data from the table and speak to that

point.

DR. SHALIT: I just want to mention that in the comparison to the SEER database, there are some limitations because we have prospective clinical data and we're comparing it to cross-sectional data, which is representing U.S. rates. We had global. There's also the bias of in the clinical studies being checked and examined every 4 weeks.

Regarding the numbers -- can you put the slide up, please? Of the SEER comparison? Because this --

DR. GEORAS: In your presentation, I think you said --

DR. SHALIT: That it was comparable.

DR. GEORAS: Right.

DR. SHALIT: Right. So again, the expected rates according to SEER were nine cases. We had 12 cases. The standard incidence rate was 1.3 with a wide confidence interval. And again, we believe that a more accurate view of the cases is excluding the cases that were diagnosed within the first six months of treatment of reslizumab since we believe

these were preexisting conditions.

Once we took off these cases and compared to the expected rates, the numbers fell below 1, still with a confidence interval which is wide, which is wide, which is partly based on the limitation of this comparison of a large database to very limited data with rare events.

DR. SHAH: And if I could just follow that up. While the preclinical studies are not always completely conclusive for the risk to humans, we did do a carcinogenicity study with this compound. And in that study, there have been shown that other drugs that are broad immunosuppressive agents do show a slightly higher risk of malignancy in that model. And in our case, we didn't see any evidence in the carcinogenicity studies of a fact on malignancy with reslizumab.

So we do feel fairly confident that, while I recognize the controversy on eosinophils and malignancy, our data certainly with the limited data we do have is not consistent with a causal relationship in that regard.

DR. OWNBY: Dr. Brittain, do you want another --

DR. BRITTAIN: I just wanted to follow up on the previous slide, which is gone now. Can we get that up?

I guess I'm not understanding the logic of excluding the six in the early phase when you're comparing it to an expected rate because the expected rate, we'd want to know about all the background. I understand perhaps when you're making comparison to placebo, you might want to look at it that way. But I don't understand it in this context when you're comparing it to a background rate of overall.

DR. SHAH: Right. I think as Dr. Shalit -- these comparisons do have limitations. One of the things we do in a clinical trial is we monitor these patients very closely, and they're always been seen regularly, which is not happening in the real world, as we know.

So there's always this bias for over-diagnosing in a clinical trial because of that

close monitoring of patients. They're much more likely to complain of -- because we ask them if they have any problems or complaints, and of course, if they had some unrelated complaint that just happened to occur during the trial, during the visit, it could be flagged up. And then the investigator would do a study to understand what could be causing it and could find a cause during the trial.

In the real world, the patients are very reserved about going to doctors. So you may not see the same degree of bias because it's not being closely monitored for patients. And this is what we believe is going on in that imbalance. We're in a trial setting. Patients are monitored very closely.

If you look at it in the context of the SEER data, even if you don't adjust for that, it is well within the confidence interval of what we would expect.

DR. OWNBY: I have Drs. Yu, Connett, Greenberger, Stoller, and Voynow in that order.

Dr. Yu?

DR. YU: Thank you. I have three questions and one comment. My first question is related to the slide CS-33 on page 53. And it's in the safety summary, and this is probably just a clarification. And it said there are 253 children enrolled or studied under all these trials.

From my reading -- correct me if I'm wrong -- most of those adolescents in those trials are healthy children that enrolled for the pharmacokinetic studies -- is that correct -- versus the difference when you're really enrolled in 3081 to 3084, those kids would have more comprised health condition with asthma.

Is that correct?

DR. SHAH: Actually, the children who were enrolled in those 253 came either from -- we had a program in eosinophilic esophagitis, which is a very common issue or not -- it's a common problem for kids specifically and also in adults, but it is a problem that's very eosinophilic specific and causes, again, difficulties for children related to

GI symptoms.

There's a lot of overlap with asthma and allergies in that group of kids who have eosinophilic esophagitis. And indeed, over half of the kids who have the eosinophilic esophagitis had concomitant asthma. So we do believe that the safety data in that population is relevant for understanding the safety of reslizumab in the kids.

There were also children and adolescents, so there were some less than 12 years of age in that. I think about half were less than 12 in that group. And some of those children were treated up to three years, about 64 of them. And we even have some -- because many of them continued on compassionate use, we now even have a handful of kids treated up to seven years with reslizumab.

DR. YU: So my question now is, in study 3081 and 3082, 3, all the screening criteria is eosinophils count greater than 400. So among those 253 adolescents, how many percent of them have the ES count less than 400? I'm just curious.

DR. SHAH: So of the 253 children or

adolescents and children, how many were less than 400?

DR. YU: Yes.

DR. SHAH: I don't know if we have that number. I'm sorry. But what I will say is that for the EoE studies, there were no eosinophil thresholds for inclusion in those trials. And therefore, I would anticipate most of those children will be much less than 400.

DR. YU: Thanks. My second question is related to your slides on page 23, C-19, and you have a comparison of U.S. doses from different -- that basically, there were three doses, 0.3, 1 and 3, and you looked at the maximum reduction in blood eosinophils. And I was just wondering if you have looked at the different doses, and particularly those three doses, for other primary endpoints and secondary endpoints.

The reason I'm curious -- I didn't see, if I missed it. The reason I'm looking at it is because for consumers, we definitely like to have the smallest dose that can be effective and be safe.

So it's common sense. So I'm just wondering if you have any comparisons among those three doses to show it.

DR. SHAH: So if you go to the next slide, which was in the presentation, it actually looked at the efficacy across the dose using the same modeling. And I would like to reiterate the point that Dr. Zangrilli made, that the 0.3 milligram, as you see in this analysis, which is looking at lung function and ACQ, which is a measure of asthma control, you see there that the dose that provides the biggest treatment effect is the 3 milligram per kilogram dose. And this modeling includes over 900 patients that were included in the reslizumab program in developing this model.

So it is a very robust way to answer this question of is the dose adequate for benefit. And the reason the 0.3 is not as good, it's partly because we did have other trials, early trials as Dr. Zangrilli reviewed, that looked at those dose where we saw no treatment effect even in the patients with eosinophilic-driven disease.

Therefore, we conclude that I think the 3081 study may be a bit overstating the effect of that dose in terms of the FEV1 improvements we saw, and this model is better looking at the totality of data and giving us a better understanding of the dose relationship between the 0.3 and the 3 milligrams.

DR. OWNBY: Excuse me. Dr. Platts-Mills, do you have a follow-up on this slide, particularly?

DR. PLATTS-MILLS: Yes, follow-up on CE-19. Is that real data or calculated data?

DR. SHAH: So let me have Ms. Mary Bond, our clinical pharmacologist, walk you through this.

DR. PLATTS-MILLS: And an additional question, do you have any basophil data on parallel effects of the dosage?

DR. SHAH: I don't believe we've looked at basophils impact with this therapy.

DR. PLATTS-MILLS: People have just started thinking about whether you can actually look at levels of basophils. They've been ignored; peripheral blood basophils.

DR. SHAH: Sure.

DR. PLATTS-MILLS: Because the advantage of your using peripheral blood eosinophils is obvious. It's incredibly important to normal practitioners because you can actually get the results as opposed to many other things. But basophils, it's possible we could also use.

DR. YU: Finished? My third question is related to your slides on page 27, CE-28. There's a ratio when you compare the reduction of asthma exacerbation and also the FEV1 and other on page 28 and 29. There are concerns about misclassification bias. I should try to learn it. I try to understand is there any way you can put a range of your estimate on those ratio or change due to the misclassification biases?

DR. SHAH: I'm not sure I'm understanding your question. When you say mis --

DR. YU: It's all like make uncertainty of your bar just due to the misclassification bias.

DR. SHAH: Are you referring to the oral corticosteroid imbalance?

DR. YU: Right, right.

DR. SHAH: Yes, absolutely. We looked at the effect of that on the analysis, and we found there was no difference in the effect size when we adjust for those imbalances. So the effects are very robust no matter how you analyze this data.

DR. YU: Thank you. My last comment is it just bothers me. I'm reading your addendum that you submitted to FDA and shared with us regarding the collection of anaphylaxis data, and I hear this through your presentation that anaphylaxis is a known risk for this kind of medication.

For consumers, anaphylaxis is a very serious risk. And I was just wondering why if this is a known risk, recognized early on, why there is not collected -- during specified in phase 3 study protocols and there's in CRF incorporated. That aspect just bothers me.

DR. SHAH: So as I explained, these physicians were experts in treating -- these are respiratory physicians who understand the risks around anaphylaxis, how to diagnose it and manage

it. We follow these patients every month because they have to come in for the infusion every month. Every month, we ask them about any complaints or side effects or issues that they may have had. And we have a lot of adverse events, as you'd expect.

In a typical clinical trial, this is a good sign that you're identifying side effects or adverse events that happen normally in people as they live and are capturing those in your database to see if there's any signals between the drug and your control.

So we believe that the method -- yes, we didn't prospectively adjudicate anaphylaxis. So we didn't have the investigator say did this patient have the Sampson criteria and would have then met the criteria of anaphylaxis. But everything we did, we believe would have identified any missing cases.

We've run through a very thorough look ourselves. We had a third party do the same, and they didn't identify any other cases that would qualify for anaphylaxis. So we think we have

identified all the relevant anaphylaxis cases.

I certainly appreciate the concern for patients around risks for therapy. And as we explained, we're very committed to working with the FDA to ensure that physicians and patients understand those risks and are able to communicate that to the physician if they have any issues.

DR. YU: Thank you.

DR. OWNBY: This is our time scheduled for a break, but I still have five more people with questions. We'll take another 10 minutes and try to get through these. So please try to state your concerns concisely.

Dr. Connett, you're next.

DR. CONNETT: Thanks very much.

I have here a paper that I found by a Google search titled "Inverse Association of Eosinophil Count with Colorectal Cancer." It's from the ARIC study. It's a big study, 10,000 people plus that didn't have cancer initially. And it says, as the title suggests, there's an inverse association of colorectal cancer with eosinophil counts. And it's

somewhat dose-response curve in the sense that they split things into three tertiles and found decreasing risk with increasing eosinophil counts.

There's no reference to this paper by the sponsor or by FDA, as far as I can tell. It relates to something Dr. Georas said, also. I'm wondering if it -- well, let me have disclosure issues here.

Three of the authors are at the University of Minnesota. That's a coincidence. I have not discussed this in any way with any of the authors, and as I say, I found this paper by a Google search.

The strength of the evidence is fairly strong. The studies that have been carried out here are short term, 52 weeks for reasonable numbers of patients, but people that may be on this drug would take it would take it for years and years, I would think.

So there's some issue here of will taking this drug increase rates of colorectal cancer and possibly other malignancies and should that have

entered into the sort of balance of risk versus benefit. In both the company's presentations and in the FDA's presentations, I don't see any evidence that it has been.

So I wonder if you can address this. If the chairman might be interested, I have copies of this. If you want to make copies for the rest of the committee, I'd be happy to hand it over.

DR. OWNBY: Dr. Shah, would you like to comment, or one of your team?

DR. SHAH: Again, I think as Dr. Georas indicated, when you look at the totality of the published data on this question, it is complicated. It is controversial, meaning in some studies, there are some suggestions of associations. In other, it's the opposite. So in that particular case, obviously, it was one that suggested there could be an association.

Maybe Dr. Shalit -- okay. Dr. Zangrilli can comment further.

DR. ZANGRILLI: I can only acknowledge what you said, Dr. Connett. This particular paper, we

have seen. We've seen many papers, and we've read I think all that we can find. And I can only echo what Dr. Georas said, that there is evidence both for and against this concept that sustained eosinophil lowering could promote a malignancy. But in other cases, it seems to be beneficial not to have malignancies. At the ATS last 2015 for lung metastasis, the eosinophils appear to promote this. And when you get rid of the eosinophils, it's a good thing.

So it's very much -- I do want to acknowledge the paper. We did look at this among many others, and I can't draw a clear conclusion.

DR. OWNBY: Dr. Greenberger?

DR. GREENBERGER: Thank you.

I have a few questions. The first is for safety and the CPKs. Do you have information regarding the level of exercise in the 24 hours before the infusions as well as supplements? That's one question.

And the second is with regards to subgroup analysis, which I know have limitations, but I

would like to be shown the baseline data for the U.S. population of research subjects so I could see the demographics.

DR. SHAH: So on the first question, no, we did not monitor the exercise activity of patients during or related to the infusion. As you mentioned, CPK elevations can be associated with a lot of reasons. Most of them are related to just physical exertion and activity, and unfortunately, we didn't monitor that.

But we do know, as you saw in some of the case studies, that these patients who are benefitting from therapy were much more active, as you would expect, because their asthma was much well controlled. So we have to also be mindful of that association of increased activity and its relationship to musculoskeletal complaints.

In the context of your second question, I'm sorry. I'm not quite clear. Could you repeat that, please?

DR. GREENBERGER: This has to do with the subgroup analysis of those research subjects in the

U.S. I would like to see the demographics --

DR. SHAH: Of the U.S. subgroup?

DR. GREENBERGER: -- placebo and actively treated. I missed it, if you presented them --

DR. SHAH: No, we didn't --

DR. GREENBERGER: -- I didn't see them anywhere on anything I ever received.

DR. SHAH: So let me have Dr. Zangrilli maybe review the demographics. This is for the two exacerbation studies or the overall population?

DR. GREENBERGER: Well, I would like to see them for the two exacerbation studies.

DR. ZANGRILLI: Yes. Thank you. Slide up. These were the disease state characteristics -- you asked for demographics, which is in a different slide, but I can give those to you as well.

Regarding the overall population as far as age, sex, other demography, the U.S. was very similar to the overall population. We had an interest in this too obviously; was there some imbalance or difference in the level of control of the asthma disease state in U.S. subjects versus

the overall population that could have driven this what we consider an anomalous response.

What we see is similar levels of inadequate control as far as lung function, ACQ score, percent of patients using a LABA at baseline.

DR. SHAH: I'm sorry. I'm not sure if we answered the question. If maybe the chairperson permits, we can maybe come back to that later on. We'll try to see if we can find that data.

DR. OWNBY: Okay. Fine. We'll have --

DR. GREENBERGER: I had a question about action plans on the -- in light of -- and it has to do with the patient as an example, 782205, from table 5. This is one of the subjects who some thought did have anaphylaxis, and I would think didn't, which would lower the rate of anaphylaxis.

But the person had already received reslizumab 12 times, then has a life-threatening episode, to me, of asthma with infection. And then there's not a safety issue because she continued to get the treatment, but it is a question of action plan. And this also comes out in the Castro study

in Lancet Respiratory Medicine.

How was it determined what the action plan would be at 4 weeks if the subject hasn't improved any?

DR. SHAH: So maybe I will have Dr. Castro answer that question.

DR. CASTRO: I think it's an important point that echoes some of the earlier comments in that actually one -- there is an indirect benefit for our patients here in that they're coming every 4 weeks to see us, which in my own practice, it's sometimes difficult to get these patients into our practice and being monitored.

In all of our subjects that participated, we had a proactive action plan with those patients set and reviewed that with them. So I can't speak for outside of the U.S. Maybe Dr. Zangrilli can take about what the overall trial did.

DR. SHAH: Did we answer the question or?

DR. GREENBERGER: Well, the patient had a drop of 49 percent in the physiology and still gets the infusion. I'm wondering about why the action

plan, or what -- did you even have an action plan?

DR. SHAH: Right, and maybe Dr. Shalit can -- I believe that case that you're referring to is the one that was adjudicated by the committee but not was considered related by, I think, the investigator or us.

I think in that individual case, the event actually began before the infusion. They had a worsening asthma, which was the condition being studied. And I think the investigator felt that that had nothing to do with the therapy. It was due to a concomitant infection that patient was having. And so they felt comfortable administering the infusion in that individual despite having some clinical worsening of that condition.

Of course, that condition continued to get worse the next day, and I think that individual then was hospitalized and treated for the exacerbation and continued then to receive reslizumab for another 13 infusions with no concerns of anaphylaxis or any hypersensitivity reactions.

DR. GREENBERGER: I know, but my point is that was one aspect, but the other is the action plan. Since we're counting exacerbations for the efficacy here, what were the investigators instructed to do? When did they know to start the action plan, or when did the research subject begin the action plan? I couldn't find out that information.

DR. SHAH: You mean in terms of starting therapy with like systemic corticosteroids in relation to worsening symptoms?

DR. GREENBERGER: Or frankly, without being argumentative, doubling the inhaled steroid was in the Castro paper, and that can be interpreted as having no benefit at all based on the literature, especially for a step 4, 5 or 6 patient.

DR. SHAH: Yes, I would say that over 85 -- approximately 85 percent of the exacerbations were associated with systemic corticosteroid administration. And as Dr. Zangrilli reviewed, in that group, the effect of therapy was substantial also and actually greater. The mean reduction was

over 60 percent in the group, if you define exacerbations by oral corticosteroid use.

Again, when these studies were designed, some investigators preferred using higher dose corticosteroids before giving systemic steroids, and it was not as established how it should be managed at the time. I think now it's becoming much more clear that an exacerbation of asthma should be defined by having to need systemic corticosteroids, so that's certainly what is now commonly done.

DR. OWNBY: Thank you.

I know we're still running into the FDA time, but we'll take a couple more minutes. Several people have spoken.

Dr. Stoller, you're next.

DR. STOLLER: Thank you. I've two questions. The first regards CE-16 about which a question was asked before. I guess this is to Dr. Zangrilli. So while I recognize that the forced vital capacity is not a primary outcome measure, you offer this slide as evidence of the

superiority of 3 milligrams per kilogram over the 0.3 milligrams per kilogram. That's why it appears in your deck, I believe.

The question is a technical one. The interpretation of the forced vital capacity, which may or may not be a marker of air trapping, of course, as you suggest, is totally predicated on the quality of the spirometry test. In particular, the forced vital capacity is very sensitive to the attainment of end of test criteria or the forced expiratory time.

So my question is, what is the quality of the spirometry? What are the expiratory times comparable in the compared groups for forced vital capacity, which would be necessary to interpret it as a reliable measure as you're offering here? Do you know anything about the technical quality of the spirometry, which can be, of course, highly variable, particularly in my experience in centers not using standard criteria outside of the United States, et cetera. So comment on that?

DR. ZANGRILLI: Yes, sure. As you said,

this isn't a -- there was no statistical test applied to the comparison between 0.3 and 3. So it's numerically larger. It's not necessarily superior, but I thought it was dramatic. That's why I did highlight it.

We did ask that the sites use the ATS/ERS 2005 standard for performing spirometry. I can't -- this is an average, so it represents a lot of patients, but you're right. There would be variability here.

DR. STOLLER: Just to quibble, asking them and demonstrating that the criteria were met is not the same. So I presume there was no quality control on the measurement of the forced vital capacity then; is that correct?

DR. ZANGRILLI: No, that's not exactly correct. There were edit checks programmed into all the spirometry. So if a spirometry was whacky, exceeded a percent predicted, then it could be flagged, the site could be queried, and we could ask is it true, is it real. So there was a series of edit checks with the spirometry.

DR. STOLLER: Fair enough. But just to quibble, the identification of outliers would not identify this particular issue because the forced vital capacity underestimated by small expiratory time would not appear on the charts as a whacky measure.

DR. ZANGRILLI: Okay. Fair enough.

DR. STOLLER: The second clarifying question is simply regarding CE-25. I just want to make sure that I understand this. In 3082 and 3083, the total number of patients under 18 years was 25 in the totality of the 52-week exacerbation studies; is that correct?

DR. SHAH: That is correct.

DR. STOLLER: Thanks.

DR. OWNBY: Dr. Voynow.

DR. VOYNOW: Two questions for clarification. Let me start with the pediatric safety and slide CS-13 where really a lot of the safety data is based on the eosinophilic esophagitis studies. But this includes a dose range. So I just wanted to get a sense of what

numbers or what percentage of these subjects received 1 milligram per kilo and how many received 3 since the dose is going to be 3.

DR. SHAH: So let me have Dr. Shalit review some of that data from that trial.

DR. SHALIT: So in this study for each treatment group, there were around 57 -- between 55 to 57 patients. So in this study, 57 patients were exposed to the 3 milligrams, and we also have the open label extension in which 190 patients were treated, some of them on the 3 milligrams. Currently, I don't have the exact number. But regarding the placebo-controlled study, the 3 milligrams was 57 pediatric patients.

DR. VOYNOW: The other question I have is about slide CE-20, which we had seen before. Because this includes a modeled point at 1 milligram per kilo for the FEV1 and the ACQ 7. So I guess my question is, we didn't receive detailed data from some of the earlier studies, so is this an FEV1 that was obtained from some of the earlier studies?

If so, how many subjects? I want to compare it to like the 300 -- or I'm forgetting the number now -- from the 3081 and whether or not this was all comers or if it was restricted to the greater than 400 EOs.

DR. SHAH: So the answer is yes, in these analyses, the patients could only be included if they had either sputum eosinophilia or blood eosinophilia above 400. So it is based on that. And if you recall, there was an earlier study that looked at 1 milligram per kilogram that failed, and there was a subset of patients with elevated blood eosinophils in that study who are included in the modeling.

In addition, the model uses the exposure response relationship. And maybe Ms. Mary Bond, our clinical pharmacologist, can give you a perspective on how that's done.

MS. BOND: Good morning. Mary Bond, clinical pharmacology at Teva. As Dr. Shah mentioned, these are predictive values based on our modeling. Our modeling makes use of actual data

from the clinical trials. In particular, the 1 milligram per kilogram dose was studied in study 290. This model only included individuals who met the eosinophil criteria.

The overall model was very robust with approximately 900 individuals in the full data set. For the 1 milligram per kilogram data set, there were approximately 30, 25 to 30 individuals.

Based on the modeling that we've done, we have a good understanding via standard accepted methodology of both the PK of the drug and the PK/PD relationships, and that's how this plot is generated.

DR. OWNBY: Does the FDA have a question or comment?

DR. KARIMI-SHAH: Hi, this is Banu Karimi-Shah from the FDA. I just wanted to make a quick comment on the modeling slide. We haven't had a chance to review this model, and so we just wanted to bring that to the attention of the advisory committee. And also, while we acknowledge the way that the modeling was done or that it was

explained here, we also note in the footnote that study 3083 was not included in this model, which was one of the pivotal exacerbation studies. So I just wanted to raise that as an issue.

DR. SHAH: I was told the reason it wasn't, there was no PK in that trial. So this is a PK and a PD model.

DR. OWNBY: Why don't we go ahead and take a break now? I'm sorry. We're running late. Let's reassemble at five till, and we'll then start with the FDA presentation.

(Whereupon, at 10:46 a.m., a recess was taken.)

DR. OWNBY: I think we'd better go ahead and get started. Otherwise, people won't all take their seats. We'll now proceed with the FDA presentation.

Dr. Donohue.

FDA Presentation - Kathleen Donohue

DR. DONOHUE: Good morning. My name is Katie Donohue, and I'm an allergist and immunologist and a medical officer in the Division

of Pulmonary, Allergy, and Rheumatology Products here at the agency.

You're going to hear from me three times this morning. First, I'll begin with an overview of the program, then you'll hear from my colleague Lan Zeng from statistics about the efficacy data, and then I'll return to review with you the safety data, including some more information about the anaphylaxis safety signal and the muscle safety signal.

Next, you'll hear from my colleague Dr. Joao Pedras-Vasconcelos about how some of the aspects of the reslizumab product may affect immunogenicity, and then I'll return to recap some of the risk-benefit considerations.

Cinqair is an anti-IL-5 monoclonal antibody, and its proposed dose is 3 milligrams per kilogram IV every 4 weeks. And it's provided as a single use sterile solution at a concentration of 10 milligrams per mL.

Now, as Dr. Karimi-Shah noted, the exact wording of the indication will not be a major focus

of our discussion today, but just to ground our review of the efficacy and safety data, I want to note the proposed use for reslizumab. It's intended to reduce exacerbations, relieve symptoms, improve lung function in adults and adolescents with asthma who have elevated blood eosinophils and inadequate control on inhaled corticosteroids.

Now, reslizumab has been studied for several allergic conditions, including eosinophilic esophagitis, others, as well as asthma. And we'll touch on a few findings from the eosinophilic esophagitis trials during the safety presentation, but the focus of today's discussion obviously is on the asthma program.

There were five pivotal studies, two 16-week lung function studies and two year-long exacerbation studies, and then an open label extension study for safety.

To understand who the patients are in these trials, patients in the first three trials had eosinophil levels above 400. Study 3084 did not recruit by eosinophil level. The first three

studies included participants age 12 to 75. Study 3084 included only adults.

All participants were on high-dose inhaled corticosteroids defined as greater than or equal to 400 mics of fluticasone or equivalent, consistent with EPR-3 guidelines, and patients in the two exacerbation trials had had at least one asthma exacerbation in the 12 months prior to enrolling that required treatment with a systemic corticosteroid.

Now, exacerbation history was neither an inclusion nor an exclusion criteria for the two lung function trials. Maintenance oral corticosteroid use was an exclusion criteria for the two lung function trials. Patients taking up to 10 milligrams of prednisone orally daily or equivalent were eligible for the two exacerbation studies. This will become important during our safety discussion.

Now, patients with a history of or a clinical concern for parasitic infection were excluded across the development program. And also,

participants had to have reasonable health, including reasonable baseline laboratory values. This too will become later in our discussion.

So looking at a timeline, study 3081 was the dose-ranging study, and there were three limitations to the dose ranging for this study. First, it studied only two doses. This is geometry 101. You can define a line with two points, but you cannot define a dose-response curve.

Second, it's well understood that most asthma control drugs, for example, corticosteroids, show a dose separation for efficacy at about a twofold difference. But here, the doses tested were 0.3 milligrams and 3 milligrams, so a tenfold difference.

Third, it's important to note that the reslizumab development program essentially was conducted concurrently. The results from study 3081 could not be used to inform dose selection for the reslizumab program. The concurrent conduct of the pivotal studies also has implications beyond

dose ranging. For example, you can see that the results from study 3084, which took patients at all eosinophil levels, really could not have been used to inform patient selection for the other trials. And the simultaneous conduct of the phase 3 program also meant it wasn't feasible to adjust safety monitoring as safety signals emerged.

So reslizumab has been under development for a long time and has changed hands a few times. Teva acquired Cephalon in 2011 and was responsible for the phase 3 program for reslizumab.

The mean age of the participants ranged from 44 to 47 years. Very few adolescents were enrolled in the program. The very small size of this population will be important to keep in mind later when interpreting the safety and efficacy findings.

Participants were predominantly female. Inclusion of Hispanic and Latino participants was fairly robust, and it's worth noting that this global research program was conducted primarily outside the United States, especially the two exacerbation studies. And as such, black

participants were included in the reslizumab program at a lower rate than their representation in the U.S. population.

In terms of understanding disease characteristics, on average, participants in the reslizumab program had had asthma for about 20 years. Most had two exacerbations in the year prior to enrolling in all of the studies, including the lung function studies. Percent predicted FEV1 ranged from 64 percent to 70 percent, and reversibility was high, on average, ranged from 25 to 28 percent.

Patients in the first three studies had fairly high eosinophil counts, on average, around 650 per microliter, and as study 3084 took all comers, the average was lower at 280 microliters.

In summary, the reslizumab program included two lung function and two exacerbation studies as well as an open label extension study. It recruited a fairly severe asthma patient population, and the dose ranging was limited, did not inform the pivotal studies, as the program

essentially was conducted concurrently. Likewise, study 3084, which investigated baseline eosinophil count, really couldn't inform patient selection as it was started after the other pivotal studies.

Next, my colleague, Lan Zeng, statistical reviewer, will present her review of the efficacy data for reslizumab.

FDA Presentation – Lan Zeng

MS. ZENG: Good morning. My name is Lan Zeng. I'm the statistical reviewer for this application. I will present the statistical evaluation of efficacy for reslizumab.

I will begin with an overview of the four efficacy studies, then discuss results of exacerbation, FEV1, and a possible association between baseline blood eosinophil counts and treatment effect.

As you have already heard, there were two exacerbation studies and two FEV1 lung function studies. All studies tested the 3 milligram per kilogram reslizumab dose. Study 3081 had an additional 0.3 milligram per kilogram dose arm.

Studies 3081, 3082, and 3083 enrolled patients with blood eosinophil counts of at least 400 cells per microliter at baseline while study 3084 did not have such an entry requirement.

The last column listed stratification factors used in each study for randomization. A few patients were misclassified. Their coding for oral corticosteroid use did not match their values in the clinical database. The misclassification rate was low, and sensitivity analysis have shown that it did not impact the overall efficacy conclusion.

The primary efficacy assessment for the exacerbation studies 3082 and 3083 was based on the frequency of exacerbations for each patient during the 52-week treatment period. Results are shown here on this slide.

Compared to placebo, exacerbation rate was significantly reduced among patients administered reslizumab in both studies. The point estimate for exacerbation rate ranged from 0.86 to 0.9 per year in reslizumab-treated patients versus 1.8 to 2.11

per year in placebo patients.

The risk ratios were 0.5 in study 3082 and 0.41 in study 3083 representing 50 percent to 59 percent reductions in exacerbations under reslizumab treatment.

Similar to the primary efficacy result, reslizumab significantly reduced the rate of exacerbation requiring oral or systemic corticosteroids by 55 percent to 61 percent. The decrease in incidence of hospitalization or emergency room visit was 31 percent to 34 percent but did not reduce statistical significance.

Please note these analyses were not controlled for multiplicity. Hence, the p-values for the last three endpoints were nominal.

Exacerbation rates were further investigated by demographic subgroups. In this plot, treatment benefit is marked by a risk ratio of less than 1, which is to the left of this vertical line. For study 3082, results are consistent and favor reslizumab treatment except for patients aged 12 to 17 years. The risk ratio in this age group was

3.07 in favor of placebo. However, there were only a total of 13 patients in this age group.

In study 3083, most subgroup comparisons supported the efficacy of reslizumab. However, African American patients and U.S. patients had an average effect favoring placebo. This was not observed in study 3082. Again, the number of patients in these two subgroups was relatively small, as you can see on the right of this plot.

In summary, reslizumab is effective in reduction of exacerbation frequency. The results are consistent for exacerbation rates requiring different types of medical intervention and are also robust based on various sensitivity analyses.

The treatment effect is less noticeable in certain patient groups with low enrollment, which is not unexpected in subgroup analyses, especially in subgroups with small patient numbers.

Now, let's look at study 3081. The primary endpoint in study 3081 was the change from baseline over 16 weeks in FEV1. The estimated FEV1 change from baseline was 0.13 liter in the placebo group,

0.24 liter in the 0.3 milligram per kilogram dose group, and 0.29 liter in the 3 milligram per kilogram dose group.

Compared to placebo, patients receiving reslizumab had significantly larger increases from baseline in FEV1. Both dose groups produced a significant improvement in FEV1 during the treatment period. Their effects ranged from 115 to 116 milliliters with overlapping 95 percent confidence interval.

Please note that study 3081 was conducted concurrently with studies 3082 and 3083. Although it included a lower dose group, the study was not conducted for the purpose of dose selection.

Here's the analysis of FEV1 by demographic subgroups. In this plot, treatment benefit is marked by the difference of greater than zero, which is to the right of this vertical line. While most subgroups comparisons showed treatment benefit, point estimates of the treatment differences favored the placebo for patients aged 12 to 17 or at least 65 years. There were 10

patients between 12 and 17 years old and eight patients aged 65 or older.

Moving on to study 3084, in this slide, please note the difference between study 3084 and the other three studies. The objective of study 3084 was to examine the efficacy of reslizumab in relation to blood eosinophil counts at baseline. As such, patients were unselected for blood eosinophil counts.

Also, unlike other studies, there were no actual baseline measurements for eosinophil counts after patients were enrolled. Patients' screening values were considered as baseline. Finally, an unequal randomization ratio was used to assign treatment to patients in study 3084.

The primary efficacy endpoint for study 3084 was change from baseline in FEV1 at week 16. The primary analysis utilized the linear regression model, including variables of treatment, blood eosinophil counts, and the interaction of treatment by blood eosinophil counts.

Interaction was tested at the significance

level of 0.1. As shown here by the p-value, the treatment by eosinophil counts interaction was not statistically significant, indicating no significant association between eosinophil counts at baseline and treatment effect. However, this study was not powered to detect such an interaction.

This graph displays FEV1 change from baseline to week 16 by baseline eosinophil subgroups going from less than 100 to over 500 cells per microliter by a 100 increment. There was no notable trend indicating any relationship between FEV1 improvement and blood eosinophil counts.

Here's a similar plot according to subgroup by quartiles of baseline eosinophil counts. Again, no particular trend was observed.

In summary, study 3081 demonstrated that reslizumab is effective in improving FEV1, although results were somehow less favorable in patients younger than 18 or older than 65. Study 3084 did not find any significant association between

treatment effect of reslizumab and blood eosinophil counts at baseline, but the study may have been insufficient in terms of sample size to detect such an interaction.

Of interest, FDA performed an exploratory analysis on exacerbation rate by baseline eosinophil counts. Data were pooled from studies 3082 and 3083. Subgroups of baseline eosinophil counts are in a 100 increment. While subgroup results are consistent with the overall population, supporting reslizumab efficacy, there is no notable trend showing correlation of treatment effect with baseline eosinophil counts in the elevated range greater than 400 cells per microliter as evaluated in these studies.

Likewise, when the data is plotted against quartiles of eosinophil counts at baseline, there was no meaningful trend showing the relationship between FEV1 improvement and blood eosinophil counts at baseline.

In conclusion, reslizumab is efficacious in reducing asthma exacerbation frequency and

improving lung function. The effect of reslizumab on trough FEV1 is not shown to be associated with the blood eosinophil counts at baseline. Lower dose of reslizumab is effective on improving FEV1 but not studied for exacerbation.

Next, my colleague Dr. Katie Donohue will present safety aspects of this submission.

FDA Presentation - Kathleen Donohue

DR. DONOHUE: Now, I will review for you the safety data for reslizumab, and we'll delve into a detailed review of two important safety signals, anaphylaxis and muscle toxicity. As part of this discussion, I will note some limitations of the safety database that will inform our interpretation of these signals. The size and duration of exposure for the safety database is consistent with international guidelines.

There were four deaths in the program, three in the reslizumab arm and one in the placebo arm. All three deaths in the reslizumab arm occurred in the open label extension study. One man died of anal cancer, another had tuberculosis and

bronchiectasis at study entry and progressed to hemoptysis and died, and a 59-year-old woman with a history of craniotomy for a brain tumor died at home four weeks after her last reslizumab infusion. The placebo patient died of a fentanyl overdose one month after his second treatment.

Serious adverse events were more common overall in the placebo group. Exceptions that were more common in the reslizumab group included anaphylaxis, fall, chest pain, and general administration site events.

Dropouts and discontinuations generally were well balanced between treatment arms with the exception of discontinuations for anaphylaxis and CPK elevations, which we'll discuss later.

Common adverse events were more frequent in the placebo arm. They included asthma, upper respiratory infections, nasal pharyngitis, headache, and sinusitis.

I want to take a minute and talk about malignancy. It's a concern with any immunomodulatory therapy, and overall, it's true

that the incidence of malignancy was higher in the reslizumab group compared to placebo in controlled studies, so 0.6 percent versus 0.3 percent, as well in comparison to the SEER database.

The eight cases of malignancy observed in the controlled trials included six in the reslizumab arm and two in the placebo arm. So the reslizumab cases were prostate, two lung cancers, squamous cell, keratoacanthoma, and a plasmacytoma.

Now, to Dr. Connett's point, the two cases in the placebo arm were a case of bladder cancer and a case of colon cancer. And to my knowledge, the only case of colon cancer in the reslizumab program was in a placebo patient, and Teva can correct me if I'm wrong there.

I'd just like to note that a relative strength of the reslizumab program was that it enrolled patients with a history of malignancy. I think that took courage. Four of the 19 reslizumab patients who developed malignancy had a previous medical history of cancer, and two of them had a recurrence of their prior malignancy on therapy. I

just want to highlight those for your consideration, and you may want to take them under advisement in your risk-benefit analysis later.

As noted earlier, anaphylaxis has emerged as an important safety signal in the reslizumab program. The National Institute of Allergy and Infectious Diseases published guidelines for diagnosis of anaphylaxis in 2006, and since then, the FDA has relied on them to identify cases of anaphylaxis from adverse event reports.

There are three criteria that can be met to identify anaphylaxis. For the evaluation of new molecular entities, the agency has usually taken a conservative approach. We limit the identification of cases to those fulfilling criteria number 1 here in the red box in which skin and/or mucosal involvement are required, and they must be accompanied by either respiratory compromise and/or reduced blood pressure. And we use this criterion as it is less likely to result in false positive cases.

I do want to note that the criteria do not

grade the severity of the reaction since all episodes of anaphylaxis are considered potentially life-threatening.

In addition, any cases reported by investigators or other healthcare professionals at the bedside are accepted by the agency as cases of anaphylaxis even if the case report does not have additional detail for specific signs and symptoms.

In general, since 2006, it's been our experience that development program for drugs with a high risk for anaphylaxis, such as monoclonal antibodies, have adopted these criteria to prospectively and specifically query for anaphylaxis in a systematic manner as part of ongoing safety monitoring. This was not done for the reslizumab program. In addition, post-infusion vital signs were not reported.

Lastly, details generally for adverse events were sparse for this program. For example, time of onset of adverse event was not captured, so it's not always possible to determine whether an adverse event happened before or after an infusion on a

given day, and it wasn't possible to generate detailed narratives to investigate safety signals more closely.

Because of these limitations in the safety data, when it was clear that an anaphylaxis safety signal had emerged, the sponsor was asked to perform retrospective investigation and adjudication for anaphylaxis. And since the time of adverse event was not available in the database, the sponsor was asked to perform a broad standard MedDRA query for anaphylactic reaction either the day of infusion or the day after infusion, trying to capture sort of 24 hours from time of infusion.

The sponsor was asked to query all of the asthma studies, including both reslizumab and placebo patients. The resulting cases were assessed by two blinded independent investigators, and if discordant, were to be discussed by the full committee of three, including the chair.

Now, it's the agency's usual practice to include all cases identified as anaphylaxis by the investigator by the beside as well as those

adjudicated by the committee. Three cases were identified by investigators at the bedside, and then two additional cases, one in a reslizumab patient and one in a placebo patient were identified during adjudication.

I'm going to review some of these cases with you, and in some of these cases, we do have details about vital signs or time since infusion, but this is sort of unusual. It must have been provided in supplementary documentation. These details were not available for all patients in the database.

So the first reslizumab anaphylaxis case occurred in a 45-year-old woman 14 minutes after her second infusion. She developed dyspnea, vomiting, and flushing. She was treated with steroids, IV fluids, and antihistamines. An hour later, she had what sounds like a possible biphasic reaction in which she developed chills, tremor, pallor, and desaturated down to 89 percent. She was treated with additional steroids and IV fluids, and reslizumab was discontinued.

The second case occurred in a 52-year-old

woman who developed shortness of breath, wheezing, facial swelling, and was unable to speak. Of note, this occurred 10 minutes after infusion, and not 4 hours as was noted in the narrative sent to the adjudication committee. She was treated with IV and racemic epinephrine and prednisone. Reslizumab was discontinued.

Reslizumab case number 3 occurred in a 47-year-old woman 20 minutes after her 12th infusion. She developed pruritus, wheal, severe lower abdominal pain, and severe burning and itching in the genital area. She was treated with steroids, IV fluids, and antihistamines. This case was considered anaphylaxis by the investigator at the bedside. Reslizumab was discontinued.

Case number 4 occurred in a 52-year-old in the setting of an ongoing asthma exacerbation. After her 12th infusion, her respiratory status deteriorated precipitously, and she required intubation. The next day, she developed a rash on her arms and face. Teva does not consider this a case of anaphylaxis as the patient continued on

reslizumab, but this was the case that was identified retrospectively and adjudicated as positive for anaphylaxis by the committee.

There was one placebo case that was identified during the adjudication process and it's interesting that this case was identified by post-infusion vital signs. So this man, his blood pressure dropped from 137/81 to 77/68, was self-limited and resolved within 15 minutes.

There were two eosinophilic esophagitis trials that were included in the BLA submission. Teva identified seven potential anaphylaxis cases and attributed primarily to food allergies. My review of study reports, narratives, case report forms, and line listings from these trials identified one additional potential case. So overall by my count, there were eight potential cases, seven in the reslizumab group and one in placebo group.

I agree with Teva that most are attributable to food allergies, but there's one that I do want to discuss. This was a 6-year-old boy who had

anaphylaxis the day after treatment with reslizumab. He did have a known wheat allergy, but I think it's notable that the physicians caring for him considered it a serious and severe reaction and were concerned enough that they did not continue reslizumab treatment for this patient.

So reslizumab is manufactured in a murine NSO cell line, and this cell line synthesizes a non-primate blood group oligosaccharide, galactose-alpha-1,3-galactose known as alpha-gal. And alpha-gal has been implicated in anaphylaxis. An increased risk of anaphylaxis has been observed with cetuximab, which is a monoclonal antibody manufactured in a different murine cell line, Sp2/0.

Now, two unusual characteristics were observed in the cetuximab anaphylaxis cases. First, anaphylaxis occurred with first-time infusions of cetuximab, suggesting the possibility of preexisting sensitization. Consistent with that, IgE antibodies specific for alpha-gal were identified in pretreatment serum samples from

patients who later went on to have anaphylaxis to cetuximab. Later, mass spec identified the presence of alpha-gal on cetuximab.

Now, the second unusual feature of the cetuximab anaphylaxis signal was significant regional variability with the highest number of U.S. cases observed in the South and the East. This led to the hypothesis that tick bites might cause patients to develop IgE antibodies specific for alpha-gal.

There are three lines of evidence for the tick bite hypothesis. First, some ecological data showing that increasing prevalence of cetuximab anaphylaxis in a geographic region matching the distribution of the lone star tick. Second, the observation that IgE to alpha-gal is correlated with IgE levels for the lone star tick. And third, some prospective data showing an increase in IgE to alpha-gal after lone star tick bites.

Three of the four reslizumab cases occurred in locations where tick species implicated alpha-gal anaphylaxes are endemic. A fourth case

occurred in Thailand where we do not yet have reports in the literature of alpha-gal anaphylaxis, but new reports emerge fairly regularly, including some recently from Australia. And potentially relevant, amblyomma and Ixodes tick species are known in Thailand.

So all of the identified anaphylaxis cases tested negative for antidrug antibodies. But this is of unclear clinical significance for anaphylaxis since the assay detects primarily IgG antibodies. It's not sensitive enough to detect IgE antibodies.

So anaphylaxis commonly is observed with monoclonal antibodies in the postmarketing setting, but it is rare to observe four cases of anaphylaxis in controlled clinical trials. The mechanism by which this is happening remains an open question. So alpha-gal is one possibility, and as I noted earlier, anaphylaxis to alpha-gal can be observed as soon as the first infusion due to circulating pre-sensitized antibodies.

But classic IgE-mediated anaphylaxis to some other moiety in reslizumab is another possible

mechanism, and this has been reported for several monoclonal antibodies not known to contain alpha-gal, including rituximab, adalimumab, etanercep, trastuzumab.

Successful induction of drug tolerance to these entities supports an IgE mechanism for anaphylaxis, and that the reslizumab anaphylaxis cases observed so far occurred after the second or later infusion is also consistent with an IgE-mediated mechanism.

We're going to shift gears and talk about muscle toxicity. This is the second safety signal observed, and broadly, myopathy encompasses patient symptoms like myalgia and weakness. It also includes myositis marked by increased CPKs, and a small subset of patients may go on to develop rhabdomyolysis, which is usually defined by acute renal failure in the setting of CPK elevations with or without associated muscle symptoms.

Now, importantly, some patients in the severe asthma program will be taking maintenance oral corticosteroids, and these are well-known to

cause myopathy. But it's worth noting that steroid-induced myopathy typically is marked by muscle weakness more so than myalgia or CPK elevations.

Now, complicating the picture here is that the reslizumab safety database has an imbalance in baseline maintenance oral corticosteroid use. Namely, about twice as many patients in the placebo arm were taking maintenance oral corticosteroids than in the reslizumab arm. And this imbalance means that it would be hard to detect safety signals for which both steroids and reslizumab could play a role such as infections or myopathy. In other words, given this imbalance, it could be difficult to detect a muscle safety signal at all.

Next, I want to discuss the timing of CPK evaluations and adverse event queries relative to infusion. So it's worth noting that a priori monoclonal antibodies are not known to cause CPK elevations, and so monthly or less frequent measurements were not unreasonable in the original reslizumab development. But the concurrent timing

of the studies meant that the protocols could not be adjusted to increase monitoring as safety signals emerged.

So in this slide, you'll see that CPK was measured and then patients were given the reslizumab infusion. A month later, they would return to clinic for their next visit where they were asked to report any adverse events from the prior month.

Now, in general, CPK levels begin to rise within a few hours of insult to the muscle, peak around the second day, and if the insult is removed, fall back to normal within a few days. But in the setting of ongoing exposure to a monoclonal antibody with a long duration of action, it's possible that the muscle injury and associated CPK levels could be prolonged or even elongated. Either way, the key point is that the CPK measures we do have are probably best understood as trough levels.

Unlike steroid myopathy, the safety signal emerging in the reslizumab program is marked by

myalgia and increased CPK levels. Participants randomized to reslizumab were more likely to experience moderate, severe or potentially life-threatening increases in CPK levels compared to placebo. Overall, 18 percent of patients randomized to reslizumab experienced one of these classes of elevation compared to 14 percent of those randomized to placebo.

Though life-threatening elevations classified as greater than 10 times the upper limit of normal were infrequent overall, it's notable that the prevalence of these was about double in the reslizumab arm. If reslizumab does cause CPK elevations, given the timing of the measurements, the prevalence observed so far in the clinical development program is likely to be an underestimate.

Next, there is evidence of time dependence for the muscle safety signal. Patients randomized to reslizumab were more likely to report a musculoskeletal adverse event in the 24 hours after infusion than placebo patients. Preferred terms

included things like myalgia, chest pain, back pain, pain in extremity, muscle spasms, arthralgia, muscle fatigue, and tendonitis.

Supportive evidence for the muscle safety signal comes from two additional findings. Patients randomized to reslizumab were more likely to experience serious adverse events or discontinuations related to musculoskeletal or CPK adverse events, and not just in the 24 hours after infusion but overall, patients randomized to reslizumab were more likely to report muscle pain than those treated with placebo.

Now, the heart of Teva's argument is that the CPK imbalance is due to an imbalance in baseline levels, and this case would suggest there's something to that argument. I want to delve into a few case descriptions to illustrate our discussion, and I need to call your attention to the fact that unfortunately, the scale of the Y-axis for these CPK levels is different for these cases and the font is tiny, so I'll walk you through it.

Normal baseline values were an inclusion criteria, but the first case is a 29-year-old woman who enrolled in the study with a baseline CPK level of above 22,000. CPK levels normalized at first and then again rose to 18,000. Her urine tested positive for hemoglobin but also some red blood cells. Renal function was normal, no associated muscle symptoms, and she continued on reslizumab treatment.

So if all the baseline abnormalities looked like this and all the CPK abnormalities looked like this, we probably wouldn't raise it as a safety issue. A lot of them looked like this.

So this patient, it's true, had a minor elevation in her CPK at baseline, but after her second infusion, her CPK spiked above 15,000 and then eventually did return to slightly above baseline for subsequent treatment. Her renal function remained normal. She had no concomitant muscle symptoms, and she did continue treatment.

There was one case reported by an investigator as rhabdomyolysis. This was a

23-year-old man whose CPK levels spiked to 6,940 after his second infusion of reslizumab, and this occurred after an intense weightlifting session. But he too had normal renal function and continued on reslizumab.

A fourth case occurred in a 35-year-old man who had a normal baseline CPK, but after his second infusion, his CPK spiked to 1,263, which is about six times the upper limit of normal. And this was accompanied by severe back spasm. Now, of note, this patient was recruited at a site that was subsequently terminated for GCP violations, and his data were excluded from the safety database and the other analyses I'm presenting here today. We don't know what his other lab values were.

Though there was one case reported by an investigator as rhabdomyolysis, it does appear that none of the patients with CPK elevations went on to develop acute renal failure. All recovered, and most were able to continue on reslizumab therapy.

It's worth exploring the statin myopathy example here. Muscle problems were fairly rare in

the original statin clinical trials. It was in the postmarketing setting that reports of myalgia, weakness, and CPK elevations became more frequent. There were also reports of rhabdomyolysis, including some fatal cases.

And it's important because this safety signal was found to be dose related. High-dose statin therapy is associated with increased risk of a muscle safety problem.

So moving on, very few adolescents were included in the reslizumab program. As such, it's possible that the imbalance you're seeing here in adverse events is due to chance. However, we must note that across many symptom organ classes, adolescent patients randomized to reslizumab did report more adverse events than those randomized to placebo, and this will be important to keep in mind during our risk-benefit discussion later for this age group.

I will note that the nature of the adverse events was typical of what you'd see in an adolescent population like in a nurse's clinic.

It's just slightly more frequent in the reslizumab group.

In terms of safety during pregnancy, no pregnancy registry is proposed. The preclinical data showed no adverse reproductive toxicity signals. There were 10 pregnancies, 8 in reslizumab, 4 live births with no malformations, one physiologic neonatal jaundice case, 2 elective abortions, and one case with missing data, and no data are available on lactation.

In summary, anaphylaxis and muscle toxicity have emerged as important safety signals in the reslizumab program. It's worth remembering that our current estimates are potentially underestimates given some of the limitations that I've noted for you in the safety database.

For the anaphylaxis, these limitations include a lack of post-infusion vital signs, retrospective ascertainment of anaphylaxis cases, and somewhat scant detail in the adverse event reporting. For the muscle safety signal, the timing of the CPK measurements suggest that the

elevations we are seeing are perhaps best understood as trough measures, and again, this 30-day recall window for adverse events may have led to underreporting.

Lastly, it's worth remembering the statin example. Especially for the muscle safety signal, it's possible that a lower dose could have a better safety profile, but this was not investigated.

Grappling with uncertainty is a necessary part of all scientific progress. It's part of the conversation for every regulatory decision we make. Today the members of the advisory committee are faced with a bit more than the usual of uncertainty in evaluating the safety database for this program. One of my challenges has been to define for you in some detail the scope of that uncertainty and how that might influence your understanding of the safety signals that have emerged.

Next, you'll hear from my colleague, Dr. Joao Pedras-Vasconcelos, about how some aspects of the reslizumab product may affect immunogenicity.

FDA Presentation - Joao Pedras-Vasconcelos

DR. PEDRAS-VASCONCELOS: Good morning. My name is Joao Pedras-Vasconcelos, and I work in the Center for Drugs, the Office of Biotechnology Products. I am the main immunogenicity reviewer for reslizumab.

My office, OBP, in addition to reviewing immunogenicity, also reviewed the product quality for this BLA, and on this slide listed are the various OBP team members that participated in the review.

I would like to begin my presentation with a brief review of the product. Reslizumab is a humanized IgG kappa monoclonal antibody, which is produced in murine NSO cells. As has been mentioned in earlier presentations, NSO cells similar to other murine cells or production systems have the ability to add alpha-gal during protein glycosylation. I shall discuss this in more detail later in my presentation. Reslizumab itself is end glycosylated in the Fc region of the molecule. The drug product is supplied to sterile solution at 10

milligrams per mL.

I would preface my presentation on the immunogenicity of this therapeutic monoclonal by explaining the possible clinical concerns when a biologic drug induces antidrug antibodies, which are commonly abbreviated as ADA. First and foremost, there could be an impact on safety due to hypersensitivity reactions such as what is observed in the current program.

Next, there is a potential impact on efficacy where the ADAs are able to either enhance or decrease efficacy by changing the half-life or the bio distribution of the product. Lowering the risk class of those ADAs, they change PK and/or PD of the product. And lastly, there are cases when antidrug antibodies, despite being present, appear to have no discernible impact on safety and efficacy.

A few words on the antidrug antibodies assays used by the sponsor. The FDA recommends a stepwise approach to monitor immunogenicity through bio therapeutics beginning with a sensitive

screening assay capable of detecting all antidrug antibody isotypes. This is followed by a more stringent confirmatory assay to eliminate false positive samples.

We also recommend the development of a titering assay to provide information on the magnitude of the ADA response. Lastly, we request that all confirmed ADA positive samples be tested for neutralizing capacity, using a sensitive assay reflective of the mechanism of action of the product.

The applicant followed the recommended stepwise approach to the evaluation of reslizumab immunogenicity. They provided information on validated screening confirmatory and titering assays. The sponsor analyzed the pivotal clinical trial samples using these validated assays. The assays used a bridging ELISA format and have a reported sensitivity of 22 nanograms per mL using a monkey anti-reslizumab polyclonal IgG positive control antibody.

This sensitivity is well within the

recommended levels by the FDA for the detection of IgG responses, but is insufficient to detect rare isotypes such as IgE, which typically requires sensitivity below 5 nanograms per mL.

The assays also have an acceptable level of drug tolerance, which is defined as the ability of an assay to detect a positive ADA signal in the presence of drug in test samples. The reported drug tolerance for the assay is 144 micrograms per mL in the presence of 500 nanograms per mL of the positive control.

This is acceptable as all the average steady state drug concentrations were less than 100 micrograms per mL. The applicant is currently developing a neutralizing antibody assay, so no information is available as to the neutralizing potential in confirmed ADA positive samples.

Next, I shall discuss the immunogenicity results obtained in the pivotal clinical trials. In the pivotal reslizumab 3 milligram per kilogram placebo-controlled studies, a total of 5.4 percent of the subjects were treatment emergent ADA

positive, which comes to around 53 and 983 patients.

The titers were low in nature, ranging anywhere from one to one to one to 106. Fifty-one percent of these ADA positive subjects experienced transient responses, which is defined as testing positive at only a single time point.

A few words on the open label portion of the program. In this portion, 4.8 percent of the subjects were treatment emergent ADA positive, which comes to around 49 in a 1,014 patients. The titers were even lower than in the earlier phase, ranging from 1 to 2 to 1 in 33 with 41 percent showing transient responses, again defined as a positive or single time point.

Importantly, ADA positivity was not associated with loss of efficacy, and there was no observable impact of ADA on PK/PD. Overall, there were similar adverse event rates for ADA positive and ADA negative subjects.

With regards to the two main safety signals discussed in earlier presentations, the

anaphylactic reactions and muscle toxicity, as reported, both were more common in reslizumab-treated compared to placebo-treated patients. The four patients with treatment-related anaphylaxis tested antidrug IgG negative, but were not tested for product specific IgE. The product specific IgE is currently under development by the applicant.

As to the increased muscle toxicity observed, a brief comment, while myalgia is often observed with therapeutic monoclonal antibody infusions, elevated CPKs are not. Currently, the mechanism for the CPK elevation is unknown.

Now, I want to discuss with you the possible product quality attributes that may contribute to observed hypersensitivity. Firstly, as was mentioned several times today, reslizumab is produced in the murine NSO cell line, and this cell line along with other murine cell production systems is able to add alpha-gal side chains to nascent glycoproteins.

A second possible factor could be the presence of murine-derived wholesale protein

impurities, which could trigger hypersensitivity responses in sensitive populations. Thirdly, reslizumab is also an IgG4 antibody, and IgG4 immunoglobulins have an unstable disulfide bond and can break down into half antibodies primarily under acidic pHs.

In vivo, IgG4 half antibodies can reassemble with other IgG4 antibodies of different specificities and form bi-specific immunoglobulins. Whether this could contribute to enhanced levels of anaphylaxis is unclear at this time.

A few words on the xenogeneic alpha-gal epitope. As described earlier, the proper name for the carbohydrate is galactose-1,3-galactose, and this form of sugar is present in most mammals. The ability to add this oligosaccharide to nascent carbohydrate chain is mediated by the enzyme alpha 1,3-galactosytransferase abbreviated as alpha 1,3-GT.

Alpha 1,3-GT is absent in old world monkeys, apes, and humans due to nonsense mutations in the gene encoding for the enzyme in these various

species. This is thought to have occurred several million years ago in a common ancestor. The number I've actually seen is 40 million years ago when there was a split, old world monkeys.

Thus, we humans are not immunologically tolerant to alpha-gal. It has been estimated that as much as 1 percent of total immunoglobulins in our circulation can bind to alpha-gal. The isotypes of these anti-alpha-gal antibodies are primarily IgG2 and IgG1, but IgA and IgM immunoglobulins are also detected.

As was mentioned in a previous presentation, some individuals also develop anti-alpha-gal IgE antibodies primarily as adults, and these antibodies have been associated with tick-borne allergies, allergies to meat products and to at least one therapeutic monoclonal antibody, cetuximab. Both the tick-borne allergy and hypersensitivity response to cetuximab show a regional distribution with higher prevalence in the Southeastern United States.

With regards to the location of alpha-gal on

monoclonal antibodies, the applicant has hypothesized that the site of alpha-gal side chain on an antibody molecule has an impact on the propensity of the therapeutic to trigger and bind anti-alpha-gal IgE. The hypothesis is consistent with the one posited by Van Buren, et al in a 2011 article.

For illustrative purposes, on the left side of the slide is a diagram of reslizumab, and shown in the red box is a molecular location where alpha-gal may be added. As you may recall, the antibody is a humanized IgG4. Alpha-gal is found in the Fc region of the heavy chain only.

On the right side is a figure illustrating cetuximab showing the locations where glycosylation of alpha-gal is found. Cetuximab is a mouse-human chimeric IgG1 antibody. In addition to the Fc portion of the heavy chain, alpha-gal is also found in the FAB region, more specifically in the complementary determining portion of the antibody heavy chain.

A brief comment on the recent anti-alpha-gal

ELISA Ig performed by the applicant. In that presentation or in their material, Teva reported results of their serum Ig analysis of the four treatment-related anaphylactic patients. Teva had the sample analyzed in a commercial laboratory that used a proprietary anti-alpha-gal ELISA.

The applicant tested baseline and post events here with samples and reported negative results. Due to the lateness of the submission, the FDA did not review the IgE data and is thus unable to comment. So in the context of this program, the hypothesis concerning the role of alpha-gal on anaphylaxis is still an open question.

A disclaimer about the subsequent slides. The information provided in the following slides was compiled from publicly available sources such as product insert labels. These slides will put the anaphylaxis safety signals seen with reslizumab in the context of other marketed products produced in murine cell lines.

There are currently seven marketed products produced in NSO cells, and all but one,

raxibacumab, have reported cases of anaphylaxis. Note that raxibacumab has had limited use as it is indicated for inhalational anthrax, and so may not have had sufficient patient numbers for anaphylaxis episodes to have been observed.

Cetuximab, the most well-known case for alpha-gal linked hypersensitivity reactions, is produced in murine cell line Sp2/0. There are currently five marketed products produced in Sp2/0 cell line, and they all have reported cases of anaphylaxis.

So summarizing my presentation, the applicant has validated the screening, confirmatory, and titering assays used to analyze the pivotal clinical samples. Overall, there is a low immunogenicity rate, around 5 percent, and ADA positive status is not associated with loss of efficacy or increased adverse events.

With regards to the anaphylaxis safety signal, the agency feels that the sponsor has not thoroughly investigated the root causes of anaphylaxis and may still have work to do. Thank

you for your attention.

Next, you will hear from my colleague Dr. Kathleen Donohue, and she will present the risk-based benefit considerations. Thanks.

FDA Presentation - Kathleen Donohue

DR. DONOHUE: I'm just going to recap the risk-benefit considerations that will underpin our discussion today. Reslizumab demonstrated statistically significant evidence of reductions in exacerbations in two year-long randomized trials, studies 3082 and 3083.

Now, this benefit was not as clearly demonstrated for adolescents. You can see here that for those aged 12 to 17, patients randomized to reslizumab had an apparent increase in exacerbations. A priori, there's no reason to suspect that the drug would work differently in this population, and it's worth remembering that the number of adolescent patients included was very small, 13 in study 3082 and 12 in study 3083.

Perhaps the most likely explanation for this difference is chance, but the committee will be

asked to discuss whether these data are adequate to support approval in this group.

Reslizumab also demonstrated statistically significant improvement in lung function, but again, we see that this benefit was not demonstrated for adolescents. You can see here that for those aged 12 to 17, patients randomized to reslizumab had an apparent decrease in lung function.

In reviewing the safety data for adolescents across many symptom organ classes, adolescent patients randomized to reslizumab did report more adverse events than those randomized to placebo, but again, those were the kinds of ordinary adolescent problems that might be seen in a nurse's office, generally. And the most likely explanation for this imbalance also is chance due to the small sample size.

Two important safety signals emerged in the reslizumab program, anaphylaxis and muscle toxicity. Anaphylaxis is a known safety risk for monoclonal antibodies, but it's rare to observe

four cases of anaphylaxis in a clinical trial's database.

Second, evidence for a muscle safety signal has emerged. Patients randomized to reslizumab were more likely to experience moderate, severe, or life-threatening elevations in CPK, more likely to report muscle pain, and there was evidence of time dependence for this safety signal in that patients randomized to reslizumab were more likely to report musculoskeletal adverse events in the 24 hours following infusion.

Certainly, malignancy is a concern, also with any immunomodulatory therapy, and you'll want to weigh that in your risk-benefit considerations.

In summary, sort of pulling things together, a clinician who treated a thousand patients with reslizumab for a year could expect to prevent 182 asthma exacerbations and five asthma hospitalizations, but the same physician could expect to manage three cases of anaphylaxis and 46 cases of moderate, severe or potentially life-threatening elevations in CPK.

It's important to remember that given the limitations in the safety database that I highlighted earlier, our current estimates for the risk of anaphylaxis and muscle toxicity could be understood as potential under-estimates.

Today, the members of the advisory committee are being asked to weigh the evidence for efficacy and safety in light of the strengths and limitations for the reslizumab program. Reslizumab has provided evidence of efficacy for reducing exacerbations and improving lung function in adults. But anaphylaxis, muscle safety, and malignancy have emerged as concerns.

In addition, it's worth remembering that a lower dose of reslizumab demonstrated efficacy in early trials but was not studied further. It's unknown whether a lower dose could have a better safety profile. We anticipate a lively discussion and look forward to your questions.

Clarifying Questions to Presenters

DR. OWNBY: Are there any clarifying questions for the FDA or the speaker? Please state

your name for the record before you speak. If you can, please direct your questions to a specific presenter.

DR. COOK: Dr. Cook for Dr. Donohue, a couple of clarifying questions. What do you think is the minimum clinically relevant change in FEV1? It goes to the dose finding as how much difference, and then the same might be said for the reduction in exacerbations.

DR. KARIMI-SHAH: Hi, this is Banu Karimi-Shah from the FDA. You're asking what we consider clinically relevant for improving FEV1?

DR. COOK: Right.

DR. KARIMI-SHAH: So we don't have a number that we tout as clinically relevant, but I think it is notable and I think the pulmonologists and allergists on this panel will agree with me that in this population of patients, both doses were showing an improvement of greater than 100 mLs in FEV1. So that is sometimes a number that is thrown around, but we don't have a number that we rely on.

DR. COOK: That's close enough in the

ballpark, what I'm looking for. Thank you.

DR. OWNBY: Dr. Greenberger.

DR. GREENBERGER: For Dr. Donohue to clarify the laboratory findings, CPK elevations. I asked earlier about the level of exercise, and the sponsor could not -- apparently, they didn't record exercise. And yet, it sounds like from your comments, you're closer to cause and effect of the drug and the laboratory tests. But are you actually saying or implying there's a cause and effect here?

DR. DONOHUE: We do see an imbalance in CPK elevations in the randomized trial database, and so that's generally considered pretty high level evidence.

DR. GREENBERGER: But is it -- I mean, it's in the absence of knowing what the level of exercise was, and we had one case with weightlifting, which you mentioned appeared to be related as an explanation.

DR. DONOHUE: It's certainly possible that it's a spurious finding and confounded by baseline

exercise levels, but as you noted, we don't have any data one way or the other about confounding factors like exercise.

DR. CHOWDHURY: Dr. Ownby, may I comment?

DR. OWNBY: Yes.

DR. CHOWDHURY: Just a point of comment here. Generally, when we see a controlled trial, we assume the variables are controlled, including exercise, until we believe for whatever reason the persons taking the antibody would suddenly exercise more, which is unlikely to think with the case. So when we see a imbalance in a control trial, usually the variables are thought to be already controlled for, in this case, including exercise. Thank you.

DR. OWNBY: Dr. Morrato, I believe you're next.

DR. MORRATO: Thank you.

I have two questions. So in the questions that we're supposed to consider in our discussion, there's one about the role of blood eosinophil counts in determining the target patient population. I didn't see as much of that discussed

in your oral presentation, so I wanted to explore a little bit on that.

In the briefing materials, there's a point made that although the trial eligibility criteria were at 400, the effect was that they were closer to 6 to 700 cells per microliter. So are we to consider that or not?

I know in the recently approved labeling, I know we're not talking indication, but it talks about an eosinophil phenotype. Is that what you're wanting us to discuss and explore, those kinds of relationships? Because it does relate to that paper that I mentioned earlier, which is now looking at population-based data and so forth.

I know there's probably a desire on the agency's part to give an umbrella kind of language that makes it easier to think about these products in practice, but what do you want us to be commenting on when it says "role of blood eosinophils"?

DR. CHOWDHURY: I will take the question here because this is a pretty general topic that

you are raising, and whatever you discuss in regards to eosinophil count to efficacy, we would like to hear that. And we are not necessarily putting out anything specific to put out because the trials here that we saw all enrolled patients with the preset eosinophil cutoff of 400. So the spectrum of counts is not there to link to exacerbation.

DR. MORRATO: Right.

DR. CHOWDHURY: And the company makes a point that they need that 400 to link to the dose and to link to eosinophil in the sputum. So there is not really a spectrum of counts to look at. And the one study that was done to look at the spectrum, we do not really see any lung function changes based on eosinophil count.

On the other hand, we should also keep in mind the drug targets eosinophil, and the scientific reasons -- in asthma is quite well studied.

Another confounding factor is these patients are taking steroids, and steroids are also known to

cause eosinophil count decrease. So that's the reason we tend to avoid getting into specific count because if you look at even the company's presentations earlier on with some numbers, if you pick a number, then certainly you're going to leave some patients who potentially could benefit who would not get the drug.

Also, when a patient is being considered for treatment, chances are pretty high the person may actually be on a steroid, which can confound to reduce eosinophil count. So we tended to agree in some ways with the company's side of eosinophil phenotype.

Another product that we discussed here, which was approved, did not actually say a count in indication; rather, it's eosinophil phenotype. And when you say eosinophil phenotype, it is not really a blood count because blood is a surrogate measure as we heard. It really is what is in the lungs, and we aren't able to measure that. And one can get to the eosinophil phenotype by sputum if somebody has it, by lack of or response dependency

on corticosteroid if they have it, or often in clinical judgment, a person cannot be taken off steroids, but they don't have eosinophil count, which is above the threshold.

So we tend to go with the eosinophil phenotype and not necessarily as a blood being the only place to look for defining the phenotype. Thank you.

DR. MORRATO: So that clarified what you were trying to get us to discuss. I won't go further there.

The other question was related to the safety data and the signals that you're noting, and I was hoping maybe you could -- you provide good context, and I really liked the last slide that you added where you're putting per thousand patients. That's a really nice way, and I know the agency is working on that kind of presentation.

Are we to think of this in terms of if we agree or disagree that there's a signal, or are we to think of it -- I mean, obviously relative to the benefit -- or are we also asking comment on, okay,

now that you have this signal, what's the postmarketing pharmacovigilance program going to look like in terms of either better understanding the risk of the signal, what data is being collected postmarketing.

Have you given thought on that? Because I know that varies if it's a statin, then there's a very prescriptive case reporting that comes with those cases. And is this meeting that threshold that this product should be collecting that same kind of information postmarketing?

DR. KARIMI-SHAH: This is Banu Karimi-Shah, and I can answer, try to address your comments. So I think the easy answer to your question is that we'd like you to discuss both things, but I think as far as we've sort of been able to glean from our review of the safety database, we think that these signals are present.

So if you disagree, we'd like to hear that, but I think that regardless, for example, of the mechanism of anaphylaxis, it's there. So we don't question the presence of the signal. There may be

conduct issues with the way the CPK was measured and the baseline values that perhaps question whether this is a real signal or not. This is the data that we have, so I think we don't question the presence of these signals.

I think what we're asking the committee is to take into account the way that these signals were evaluated and sort of weigh them with the benefit of the drug to really decide whether or not this drug's risk-benefit evaluation supports the approval of the drug.

Then, if that's where you come out, then these additional issues of what should be done in the postmarketing setting are very important comments that we would appreciate.

DR. CHOWDHURY: I would also add to that -- with our equation that you're bringing up is the dose issue. We understand why this particular 3 number was chosen to target decreasing the eosinophil count. We also understood from the discussion here the eosinophil count may potentially have some safety concerns with

malignancy. It is unknown, depending on how you look at it.

Also, we have a small database, which is always the case in a controlled trial, and what else is in the safety we are missing that we will not see in a controlled trial.

So that's the reason we from the agency's side pay particular attention to what dose should be approved, not necessarily lowest effective dose, which may be an arbitrary number, but something that is reasonable and not way up in the dose-response curve, not only to avoid safety that you're already potentially seeing here -- arguably the CPK elevation that the company may have different opinions on, but you can discuss this.

Malignancy is a potential issue that you're bringing it up, and immunosuppression with this molecule is always a possibility. We do not see immunosuppression with this particular molecule here, but another IL-5 drug, which was approved recently, has infections as one of the warnings, which we're not seeing here.

So these are unknown safety signals that is somewhat in our mind with the appropriate dose selection is also consideration that we're asking you to opine on. Thank you.

DR. OWNBY: Dr. Georas, I believe you're next.

DR. GEORAS: I'd like to ask for your perspective, if you could provide comments from the agency's historical experience on two fronts. One relates to how frequently do you see a drug development program where phase 3 is conducted concomitantly with dose finding? Is that a frequent practice or not?

DR. CHOWDHURY: Maybe I can take this question, and some of my colleagues can also answer this. I cannot really say for the whole agency. I'll probably limit myself more in the asthma and COPD program. And mostly a dose selection is informed by some basis, and those bases often are scientific rationale, some PD experience and often small dose-ranging studies.

In some situations when you're looking for

exacerbation, for example, as an endpoint, you cannot really do a dose-ranging study for exacerbation because it will take a year or so. So in those situations, it is not uncommon to put more than one doses in the phase 3 program. That is common that we see in programs like that.

In this situation, we have actually an FEV1, which is relatively small; study can pick it up in a small direction. With an FEV1 endpoint, typically we see actually dose-ranging studies early. Look at the FEV1. If it improves, then go with the phase 3 program, if you would, in form with the phase 2 program.

So we actually put quite a bit attention to dose ranging if it is FEV1, which was the case here, or in the phase 3 program to actually explore more than one doses in asthma and COPD programs where the trials are quite long. So we have risk-benefit assessment, which unfortunately, in this situation, we do not.

At the same time, we do want to acknowledge the company has given some thought, some reasoning,

why they picked up the 3. It didn't just come up from nowhere. So keep that into consideration as you discuss this. Thank you.

DR. GEORAS: Could I follow that up with a quick question about the malignancy concern that was raised where I gather the concern of the agency was not as great as perhaps some of the questions we raised. Is that based on your prior experience with biologics, where the signals that we saw today have been in seen in other biologics that did not turn out to have a malignancy risk in postmarketing?

I'll also say that the six-month or the fact that the sponsor enrolled patients with a history of malignancy, I agree is a strength, but I don't view the early onset of cancers that patients were previously diagnosed with as a way of exonerating the drug. In some ways, if we think eosinophils are involved in tumor surveillance, I don't think that that should give us reassurance.

So I guess the question would be your perspectives based on other biologics, maybe, in

asthma or rheumatologic disease.

DR. CHOWDHURY: Again, I can take this question and make some general comments. I think generally assessing malignancy a priori in a clinical program to either define the risk or exclude the risk is often limited because of the small sample size that typically are in these programs.

However, we do care and do want to look at malignancies, and you asked for examples in other areas outside asthma and COPD such as TNF blockers or other cytokine blockers in the TNF pathway. On those programs, we often see malignancy in a trial of this magnitude. We do see them.

On those situations with blocking like the Th1 pathway or innate immune pathways, one can expect to have malignancies. It is not necessarily completely out of the expectations. At the same time, the disease confounding factors with multiple immunosuppressives in those sort of diseases also becomes confounding.

In the asthma and COPD kind of program,

specifically asthma, with IL-5 blocking, I think the a priori risk of malignancy is unknown. We see a malignancy imbalance, no question about that, and we pointed it out. But we did not really raise it as a high level signal of a safety because of the nature of malignancies, the timing that happened, and what you have heard here.

At the same time, we don't want to discount that. So certainly you should bring it up and discuss this.

As far as prior experiences, we had IgE blocking monoclonal antibody, this was approved plus-10 years ago, and that actually in the clinical program had a malignancy imbalance, something of this nature of varieties of count kind of scattered imbalance. And it was not very significant, but close.

So come back to SEER database, it was done at that time, the imbalance was really not necessarily that pronounced. The malignancy ended up being a warning in the product label. That led to a postmarketing study that was done over

multiple years, and that malignancy signal actually was not proven for the molecule.

The point here is this IL-5, IgE, these pathways, it's very difficult to, a priori, pinpoint as a pathway of malignancy. At the same time, we don't want to discount completely the trial data that you're seeing here.

Again, looping back to infections and malignancies are usually thought to be dose related, how much immunosuppression do you need? Do you need the maximum? And generally, in the dermatologic field, we actually pay quite close attention to it and don't go to the maximum dose.

DR. OWNBY: Thank you.

Dr. Platts-Mills, I believe you're next.

DR. PLATTS-MILLS: Thank you. Can I ask some questions about what happens in pre-visits? When a company comes and agrees with the FDA, what happened about the age group? Because 12 to 17 is a silly group. What's that got to do with reality? Twelve-year-olds are adults, and the NIH says that we can enroll people between 18 and 21 as children.

And you can't drink till you're 21. We've had two students arrested violently in Virginia this year for trying to buy beer when they were 20.

So the question is, was 12 to 17 defined as a group when the company came to the FDA and described their proposed studies? Because if it wasn't, then you can understand that there are these tiny numbers of patients. If it was described as a group at that time, one would say why on earth were there only so few enrolled?

But can I ask another question? Was the subject of sinusitis discussed? Because it's very striking that there is no increase in sinusitis. The signal for sinusitis is ridiculously low given that these patients, the eosinophilic, severe asthma patients have a very high prevalence of sinus disease, and there's actually a correlation between eosinophil counts and sinus disease. And I would have loved to have seen CTs on the whole -- maybe Mario has data on CTs and whether CTs changed during this time.

But first perhaps the issue of how do you

define the age range.

DR. KARIMI-SHAH: This is Badu Karimi-Shah from the FDA. So the age range for asthma clinical trials as we review them at FDA is historical. Our asthma clinical development programs start first usually at age 12 and above. And so we include sort of this 12- to 17-year-old pediatric age group, and this has been for as long as I've been here and for a number of years before.

Why that cutoff was chosen, I agree, it does seem a little bit arbitrary, but we do go over the clinical programs with the sponsors prior to them embarking on them. But we don't have a number of adolescents that we deem as being adequate or inadequate to include in the trials.

I think it's also worth noting that we make a big argument about small numbers and the ability to trust signals, but when we have equally small numbers in subgroups that show efficacy or trend towards the same efficacy as the larger subgroup, we don't tend to question those results. So I think the argument can work both ways there, and so

I just wanted to address that.

But to your question, the 12 and above comes from all asthma clinical development programs in LABAs, ICS. And I think Dr. Chowdhury wants to add something.

DR. CHOWDHURY: I just want to add some points here. Pediatrics, as we all agree, is a vulnerable patient population, and actually, the regulations specify those as different. So that's the reason we bring it up. And a priori, we expect that pediatrics would be studied, efficacy demonstrated or enough scientific evidence produced so that we can make an extrapolation, meaning the disease is the same, which in asthma we have concluded is the same. The effect of the drug on the disease is the same, which for this particular molecule is new. We don't really have that information.

As for numbers of patients, we already know this is about -- proposing and would agree, 3 to 5 percent of total asthma patients. It's a very small number. And again, if you want pediatric

patients powered enough in the small subpopulations, you just don't have it. It is not going to practically happen.

We had the same situations with the mepo that was discussed here a couple of months ago with small numbers, and the direction was in the right side. And as Dr. Karimi-Shah mentioned, if the direction is on the same side even with small numbers, we are comforted by that. If it's on the opposite side, we bring it up for questions, and that's the reason we are asking your opinion on this.

DR. OWNBY: Dr. Tracy. Oh --

DR. PLATTS-MILLS: Sinus disease? Was sinus disease considered or discussed?

DR. DONOHUE: So I can comment that sinusitis as an adverse event was pretty evenly balanced. It was a little lower in reslizumab, 6 percent versus 7 percent in placebo, if the company wants to address some of those things.

DR. PLATTS-MILLS: I'd be more interested in whether it had an effect on outcome; that is, did

patients with extensive sinus disease do better or worse?

DR. OWNBY: I believe Dr. Castro's going to comment.

DR. CASTRO: I'm allowed to? Okay. Great.

So we carefully looked at sinusitis in the earlier study that was published in the blue journal in 2011, and clearly in that subset of patients that had a history of nasal polyps and sinus disease, there was a marked benefit with Asthma Control Questionnaire score of greater than 1 improvement there.

The subsequent pivotal trials, 82 and 83, we're still looking at that data, but there appears to be a consistent signal there in terms of improvements to patients with sinusitis.

DR. OWNBY: Okay. I realize we're cutting into our lunch break, but we'll shorten that to try to encourage discussion. I have Drs. Tracy, Dykewicz, Yu, and Greenberger, in that order. Dr. Tracy.

DR. TRACY: Kind of a general question but

also specific to this study. In the briefing packet on the agency's side, there's multiple references to protocol violations, which we really didn't discuss. And I was just wondering, first of all, how as a committee as we deliberate should we look at that, and will that affect how we view these things?

Also, is this unique to this project, or where does it fit? I kind of put that in line in my own assessment. I found it odd that they didn't get vital signs after the infusion. It kind of tells me that things aren't always -- I think actually one site was actually discontinued.

DR. KARIMI-SHAH: This is Dr. Karimi-Shah. Dr. Tracy, thank you for asking that question. So in terms of protocol violations, to your first question, in these large global programs with multiple sites, we often see protocol violations, and we often note this in our review.

As far as the protocol violations affecting our interpretability of the data, we've brought this to your attention at advisory committee for

discussion. And from that, we've concluded that despite the protocol violations, that we are relying on this data, and we would like you to interpret it in the way that it's presented.

So I think that the level of protocol violations while are present in our document, we're not raising that to the level that would challenge the interpretability of the data presented. So that's number one.

Number two, you were asking about the post-infusion vital signs not being collected. We note that as a limitation in the program, and beyond that, I don't know what else to say about that. It did limit our ability to sort of retrospectively analyze the anaphylaxis cases.

DR. CHOWDHURY: I still would want to add one point. I think that the violation that you're seeing, it varies from program to program, but given multinational program conduct across the world in different countries, this happens with every good intention. And the point is we have looked everywhere carefully, and it's another

separate process that we will employ to look at this more carefully.

But the fact that we are bringing it here simply is our assertion that these violations are not to the level to invalidate the study.

DR. TRACY: I asked the question. I've been doing these for quite a while. I don't think I've ever remember it actually being brought to this much attention. That's what kind of caught my eye. Thank you.

DR. CHOWDHURY: Okay. Thanks.

DR. OWNBY: Dr. Dykewicz?

DR. DYKEWICZ: A question for Dr. Donohue. It gets to the question of safety signals and the general statement that you made that there was no time of onset that was being recorded for some of these safety signals. Now, obviously, the anaphylaxis cases, or presumed anaphylaxis cases, were vetted more thoroughly. We were able to present data showing how many minutes after infusion the apparent reaction occurred.

But in looking at signals for

hypersensitivity reactions, it's also relevant to look not only at anaphylaxis, but things such as urticaria, pruritus, face, mouth edema, rash, erythema and so forth that were reported by the sponsor.

So is the case that those types of adverse reactions, which might be indicative of a hypersensitivity response, were not catalogued in the database as being timed versus time of administration of the drug?

DR. DONOHUE: That's correct. So in my look at the case report forms and in the actual database, I don't have a variable for time of onset of adverse event that I can look at. So I'm unclear about exactly where that additional detail came for the anaphylaxis cases. There must have been some supplemental documentation specific to those cases.

DR. DYKEWICZ: It does give you some pause for concern that if we're really trying to look at signals for hypersensitivity, we don't have the full amount of information we'd like to see.

DR. CHOWDHURY: I just want to add some points here. I think as the company is saying, I mean, if there was obvious cases of anaphylaxis, one would probably see, and that's not the case here. So it's a matter of is it possible underreporting or not? This is a judgment call.

Typically in programs like that, we do not adjudicate for anaphylaxis. Usually companies would give the criteria that is typically accepted globally, I would assume the Sampson criteria. The clinicians would be looking at these patients, I guess the criteria, to look for signs and symptoms of anaphylaxis.

Also, the timing is important because these products often have events out to 24 hours, give and take some. So if a patient is not being proactively queried or the investigator is not querying, then some of the events that may be somewhat subtle like drop in blood pressure with some skin raising, skin itching, would not necessarily be picked up.

So it is a matter of more what we are saying

is not necessarily missing of gross cases. It may potentially be underreporting.

DR. OWNBY: Dr. Yu, I have you next.

DR. YU: I have a similar question about this protocol violation, but you answered last of it. But I still have a question. Do you have a number that is, say, how much percentage that the violation that we think is acceptable or not acceptable, or are you just pretty subjective to decide?

DR. KARIMI-SHAH: This is Banu Karimi-Shah, FDA. You're asking about the percentage of protocol violations?

DR. YU: Violation, yes.

DR. KARIMI-SHAH: There is no number that is acceptable or unacceptable, and it really depends also on to the nature of the violations. And I think as you heard Dr. Chowdhury said, we did look extensively at what the protocol violations were, and we've asserted that these did not rise to the level that you could not discuss this in advisory committee today.

So we don't -- I mean, there isn't a number that beyond which the study is invalidated, and with these studies, as Teva has proposed, it's reasonable to evaluate the data.

DR. CHOWDHURY: Just to add this point, I don't think there is an issue for violation that will invalidate the studies. The program is acceptable; it is okay. And I think we should probably get moving beyond the protocol violation issues because it's a non-issue really.

The sites that we had problems, Teva looked at it, and they had GCP violations. The sites were discontinued. And we understand that we accept that it happens in the programs.

So it's a matter of what we are already laying out for you is some limitations of interpretations of the data with limitations of collection of events or not applying, a priori, some characteristics. The protocol violation issues are really not an issue for big time discussion here. If they were, we typically do not bring those programs to the advisory committee

discussion.

DR. YU: Thank you.

I have a second question, a quick question to maybe Ms. Zeng about the trial 3082 and 83. There's still this issue. They talk a lot in the FDA briefing about this misclassification, imbalance between those two and this maintenance corticosteroid use, the misclassify, so the stratification, imbalanced.

So I just wonder, when you analyze -- compare the effect of the drug in 3082 and 3083, how would that pool the differences? If you have a balance differential, you generally pooled to a null, and then others, it could be either way. So do you have any numbers that could guide us to understand how much bias, that impact the bias?

MS. ZENG: Yes, we did perform a sensitivity analysis. Should I just read the number or pull out the slides?

DR. OWNBY: Can you pull them very quickly?

MS. ZENG: The first backup slides. First

one. Yes, thank you.

So as you can see from this table, the discrepancy rate in study 3082 is 6.6 percent for the placebo group and 11.4 percent for the reslizumab group. And the discrepancy rate ranges from 4.7 to 6.5 percent in the other study.

The sponsor's analysis made adjustment for baseline oral corticosteroid use as they were recorded in the randomization strata. The FDA analysis adjusted for those factors as they were recorded in the clinical database.

The results for the risk ratio in the sponsor's analysis in 3082 is 0.5 and in 3083 is 0.41 representing 50 percent to 59 percent reduction in exacerbation frequency. In our analysis, the risk ratio for study 3082 is 0.52 and for study 3083 is 0.4 representing 48 percent to 60 percent reduction. So it's quite consistent with what the sponsor have obtained.

I hope that answers your question.

DR. YU: Thank you. I just was concerned about they could have obscured the effect of the

drug, so it sounds like maybe I missed it. Thank you.

DR. OWNBY: We still have some more questions, but we're going to go ahead and break for lunch, so remember your questions. We'll have time this afternoon to discuss them.

We'll now break for lunch. We'll reconvene again in this room at 1:15 p.m. Please take any personal belongings you may want with you at this time.

Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you.

(Whereupon, at 12:30 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:16 p.m.)

DR. OWNBY: We will reconvene this meeting of the Pulmonary-Allergy Advisory Committee. Thank you all for coming back on time. I realize there were some challenges at lunchtime.

This is normally the time for the open public hearing, but I have been informed that there are no speakers wishing to speak at the open public hearing, so that is now closed.

Someone from the FDA, one of the clinical pharmacologists, wanted to comment on a slide.

DR. REN: Hi, this is Yunzhao Ren, the clinical pharmacologist reviewer of FDA for reslizumab. I have a very brief comment for the sponsor's slide, which is the FEV1 and ACQ 7 change, the dose-response slide. That is CE-20, yes.

So this analysis was not included in the most original BLA submission. As you can see here, let's talk about FEV1 change from 0.3 to 3. You can see approximately about 100 mL change over a range of tenfold of the dose, but if you go

back -- but that's the model predicted.

If you go to the real data, the phase 3, 3081, you can go to FDA slides, stat slide page 8. Here you can see, that's the real data observed from a predefined study. You can see -- although it's not powered to do a dose-response analysis, but you can see the difference is only 50 mL. That's observed data.

So when you are generating the model, you should always consider the context. For that model generated by the sponsor, they probably include a lot of data from phase 2. And many phase 2 data, all studies, they don't have eosinophil cutoff, which here if you buy the concept which reslizumab is only benefit for those patients who have high eosinophil cells, but in that model, it includes all the populations like all comers. So that could explain the difference.

I'm also the clinical pharmacologist reviewer of the mepolizumab, so I can tell you a little bit about the program development of mepolizumab. So for GSK, they actually did very

good dose-ranging study. They call it phase 2-B or phase 3 study, which in that study, the primary endpoint is exacerbation. The study length is 52 weeks, and they studied 3 doses within a range of tenfold. But this kind of study was missing here from reslizumab. So that's it.

Clarifying Questions (continued)

DR. OWNBY: Thank you.

There were some additional questions we had for clarification. I'll take those, and then I'm going to allow Dr. Shah to comment for a few minutes to respond from the sponsor's point of view.

So I had Dr. Greenberger.

DR. GREENBERGER: Thank you. This has to do on the statistical analysis. Did you determine the median as opposed to the mean number of exacerbations? In other words, how many people were really below the average and had zero exacerbations, for example.

MS. ZENG: We don't have that data right now, but let me see if we can provide some

additional information.

DR. OWNBY: So let's move on. We'll see if we can come back to that.

Dr. Stoller, I believe you were next.

DR. STOLLER: So my question regards not protocol violations but a comment about amendment 6 on endpoint modification, which you described in the briefing document on page 64, and it regarded a change in the definition of exacerbation in 3082.

So the question emerges, how significant was that in the interpretation of the results of 3082 on exacerbation frequency since that's a major consideration for our efficacy deliberation. And specifically, I'm not used to thinking about amendments that change the primary endpoint after the study is done, which I gather is the case here. So it prompts the question, was the original endpoint analyzed and was the amended endpoint analyzed, and is there a difference between the two?

DR. DONOHUE: I would actually like Teva to address the nature of the change in the endpoint

because they had provided some additional information in their addendum to address that aspect of it, and then I will ask my colleague to address the analysis portion.

DR. OWNBY: Dr. Shah, are one of your team going to respond?

DR. SHAH: I'll let Dr. Zangrilli respond to the question on the amendment, and then I'd like to make some comments, please.

DR. OWNBY: Okay. Thank you.

DR. ZANGRILLI: Yes, the amendment actually pertains to both 3082 and 3083 because they were both exacerbation studies, and it was designed to update the definition of asthma exacerbations to one that was more conventional. The original definition, when the study started in 2010, considered lung function declines as an actual countable event.

We evolved in discussion with the FDA to define an exacerbation, as I described that, as a medical intervention as it relates to asthma worsening, because that was the amendment. It was

made when the studies were close to completion, but the databases were not unlocked. We did not have any pre-knowledge of the data, so it did not influence the analysis in any way.

MS. ZENG: This is Lan Zeng. We do have the mean frequencies of the exacerbation for each study. The sponsor's study report did provide the median, but I don't have it right now, so I'll just give you the mean value.

In study 3082, the mean exacerbation rate for the placebo group is 1.34. In the reslizumab group, it's 0.72. And in study 3083, the mean is 1.01 for the placebo group, 0.46 for the reslizumab group. I believe the sponsor would be able to provide the median data.

DR. SHAH: So I think the question also was around how many patients didn't have exacerbations, so maybe Dr. Zangrilli can just speak to those.

DR. ZANGRILLI: Sure. The question I heard was -- or the build to the question was how many patients had no exacerbations on treatment. And that proportion was always higher for reslizumab in

both of the 3082, 3083 trials. Sixty-two percent of the patients in study 3082 who were treated with reslizumab had zero exacerbations versus 46 percent on placebo, and the proportions were about the same for study 3083.

DR. OWNBY: Did that answer your question, Dr. Greenberger?

DR. GREENBERGER: Now I can think about what it means, but I thank you for giving me that.

DR. OWNBY: We've got one more clarifying question. Did you want to speak first, Dr. Shah?

DR. SHAH: Whatever you feel is appropriate.

DR. OWNBY: Dr. Platts-Mills was the last clarifying question I had -- oh, excuse me. I've got one more.

DR. PLATTS-MILLS: I'm sorry. It's very simple. How long did the patients stay in the unit after having infusions, and was it longer at the beginning or was it always the same? I just haven't heard it. Maybe I missed it.

DR. SHAH: It wasn't prespecified, but we had -- the infusion took about 55 minutes, and the

patients were usually there for 30 to 60 minutes afterwards, after the event or the infusion.

DR. PLATTS-MILLS: Did infusions continue to take 55 minutes, or do they get faster when they're used to it?

DR. SHAH: It was a range, 20 to 55 minutes. It was up to 50, depending on the individual and probably the vein and so forth.

I do want to correct a couple of points, which have been raised, which I think they're important for the committee --

DR. OWNBY: I want you to state your name again to make sure we have the comments in context for the record?

DR. SHAH: Absolutely. I'm Tushar Shah. I'm from Teva. I'm the senior VP for respiratory R&D.

First of all, the PK/PD model, we actually included that in the BLA submission, and I'm happy to provide the FDA the actual reference information and where in the NDA or BLA it's there. So it was there right from the beginning. It was included as

part of the original submission.

Second, that data was also included in the briefing materials, so hopefully some of you had a chance to review that.

There was also some miscommunication around what was done in the model. We actually only looked at the patients who had elevated blood eosinophils in that model from the earlier studies. So they were identical in terms of phenotype to the patients in the phase 3 program. And what that model did include is data from earlier studies where lower doses did not show a benefit in these asthma patients.

So when you look at the totality of data, which included over 900 patients' worth of data in that model, as I showed you in the slide, it's clear that the 0.3 milligram is not an adequate dose for showing improvement in lung function or improvement in ACQ. And we believe that model is very important in understanding what is the optimal dose for reslizumab, and that model clearly established that the 3 milligram per kilogram dose

is the optimal dose where the greatest effect is seen.

I also wanted to comment on some of the points around that we didn't collect the data adequately. As I have indicated in my comments, that we collected -- we knew every -- the day of every adverse event. That was collected in every patient. What we don't have is the minute and the seconds of exactly when an event might have occurred.

However, as I explained, these patients were in the care of the physicians, getting the infusion in a period of time afterwards. And they're already sensitized to being in a clinical trial and understand the importance of reporting adverse events and side effects.

I think I can be absolutely clear and confident that if there were clinically relevant adverse events that were related to anaphylaxis, we would have seen them in the context of how the studies were done.

Finally, I think there's a lot of comments

being made about vital signs not being collected post-infusion. And maybe I can have Dr. Adkinson come and just speak to the point about the value of collecting vital signs to identify anaphylaxis given what we know about how anaphylaxis could occur in the context of a treatment.

DR. ADKINSON: Good afternoon. I'm Franklin Adkinson, Johns Hopkins University School of Medicine. I did not participate in the adjudication of the cases done in these Teva trials, but I have considerable experience in adjudication of anaphylaxis events.

I was quite surprised and disturbed to hear this morning the suggestion made that because there was not a formal protocol requiring vital signs, for example, to be measured at the end of the infusion, that anaphylaxis was going to be missed. I think clinically, that's very unlikely because anaphylaxis is not something that can be missed. It has to be addressed if it's of significance.

But more importantly than that, it's impossible to write a protocol that tells you

exactly when to take the observations that need to be made in order to make the diagnosis and treat anaphylaxis because they can come at any time. They can come in the first two minutes of the infusion. They can come at the end of the infusion or a half an hour later.

So if you write a protocol that's inflexible and says do your vital signs at the end of the infusion and use that, you're going to miss a lot of cases of serious allergic reactions and anaphylaxis.

So having reviewed the cases associated with this product, I'm convinced that what was done was adequate to describe the cases properly for adjudication, but also that the care in documenting the cases was sufficient to assure me at least that anaphylaxis as an event or even a serious systemic allergic reaction was not missed in these studies.

DR. OWNBY: Dr. Brittain and then Dr. Morrato.

DR. BRITTAIN: I want to follow up on the dose-response model that you were talking about a

few minutes ago. I guess it would be helpful if I understood a couple of things. One, the first piece is how many people did you have analyzed in that model who were at reduced doses? How many had 0.3, how many had 1, whatever it was?

Also, is there any confidence bands around this model? I mean, we're just seeing a point estimate of these models, and I don't know how much variability there are in these estimates.

The third question is I understand that now everyone had values above 400, but because most of the lower dose patients were in phase 2, were there other differences in the entry criteria that make them different kind of patients?

DR. SHAH: So let me answer the last question first, and I'll have our clinical pharmacologist because she's the most closest to the model and understands that and can speak to some of those questions.

In terms of the patient population, in the earliest studies, they did look at medium to -- basically patients on inhaled corticosteroids

who were still uncontrolled in various means and lung function or symptom-type criteria. But they didn't specify the blood or any kind of an eosinophil requirement for those studies. So it is a broad population, and the drugs did not show a benefit in the original trials for any of these anti-IL-5 therapies actually. And it wasn't until we realized we do have to focus that we showed the benefit.

So the model is focused on those relevant patients who have the right phenotype who would then be expected to benefit.

The numbers of patients and how the model actually and variability, maybe our clinical pharmacologist, Ms. Bond, actually will get a chance to comment on those.

MS. BOND: Mary Bond, clinical pharmacology at Teva. In terms of the numbers of individuals at the lower doses, depending on which endpoint we're looking at, whether it be eosinophils, FEV1, or ACQ, for the 0.3 milligram per kilogram, it was approximately 100 to 125 individuals across the

program. And for the 1 milligram per kilogram dose, it was approximately 30 individuals.

The second question, I believe, was related to the variability. Let me just check what backup slide we need here. Slide up, please.

This will demonstrate for you a sense of the range of exposures and the range of FEV values that we saw with the 0.3 milligram per kilogram and the 3 milligram per kilogram dose within the model, and that's just the range as shown across.

Does that answer your question?

DR. BRITTAIN: I'm not sure. I guess what I was hoping to see was there -- in the model, were like slide CE-20 --

MS. BOND: I see.

DR. BRITTAIN: -- can we see CE-20? Yes, I mean, are there confident bands around these? Because I'm guessing there's a fair amount of variability here, or I'm wondering.

DR. SHAH: We don't have that specific slide that looked at that, but I think there is variability, of course, around each of those

values. Yes, of course.

But what the model is showing is the relationship with dose, which has been raised as a question, and it does, looking at all the data, support the 3 milligram per kilogram dose selection.

So I do -- just one more comment, I beg your indulgence or --

DR. OWNBY: Do you have a comment about --

DR. REN: Yes, of course, I have comment. So can we go back to the CE-20? I just have additional comment for this slide.

Here, it says, "Include studies 290 and the 5010, 81 and 82." The dosing regimen for 290 is very different from other studies, all the remaining studies. All the remaining studies have Q4 week. The 290, actually they only studied two doses. The first dose was given the first week. The second dose was given the 12th week, and that's it. And they somehow also measured FEV1 at the end of week 16.

So I'm not sure if it's optimal to put those

different dosing regimens in the same context and do modeling. That's my first comment. And my second comment is that I'm not sure if that analysis is from exposure response analysis, which actually the X-axis should be the drug concentration. And somehow the sponsor translated that concentration back to the dose. So those are my two comments.

Finally, I want to reiterate that legally, FDA does not approve a drug or the approvability issue won't be affected if the sponsor sufficiently studied a minimally effective dose or not. But from patient point of view, if this dose was sufficiently studied, as the case in mepolizumab, put in the context of efficacy and safety, in this case we know anaphylaxis does not happen in lower doses of 0.3 milligram per kilo. So it only happens at high dose. That's our concern.

DR. KARIMI-SHAH: Hi. This is Banu Karimi-Shah from FDA again. So like many of you on the panel and in the audience, I'm a clinician, and I think that we have to remember that while

modeling has its place in clinical development programs, in this development program, we have real data in study 3081, and we know what that data shows. So with all respect to the model, I think when you have some real data to rely upon, the model sort of comes in second place to that.

One more thing. Sorry, I forgot. If the sponsor could just put up CE-20 one more time, so if we sort of look at what the model is showing, as it's actually not showing us what we are seeing in the actual data, and the Y-axis here says change from baseline and FEV1 and leaders at week 16. And if we sort of extrapolate the model back to the dose of zero, you're getting a change of 90 mLs in the model.

So that's actually saying that placebo works at 90 mLs, which is what the model is saying. So I think again, with the presence of real data, the model really has to be taken with a modicum of caution.

DR. SHAH: I don't disagree the model has a role and has to be taken in the context of data,

but I also think it's important that there were studies that were done earlier with lower doses, and they are included. So these are based on real data, not just model-derived data.

With that said, I think the point about FEV1, as we've shown in our data, the effect on FEV1 is seen at 4 weeks and is fairly constant and stable from there on. And we did collect in those earlier studies FEV1 at 4 weeks, and it is a reliable way to look at these earlier studies in this model to understand this relationship that we're discussing.

As we explained, this is not -- the question of dose can be addressed. Yes, traditionally, dose ranging, I hear mepo keep being referred as an example, but if you recall, in their studies, the lowest dose on reducing exacerbations was as effective as the highest dose. So there was no dose response observed in any of those doses on exacerbation reduction in that trial.

So I think it's not, to me, convincing yet that we needed to look at a lower dose to

establish. We did do that in these studies, and it shows that it doesn't provide the benefit that we believe is appropriate and needed for these severe patients who definitely need the benefit to get the clinical improvement.

DR. REN: This is Yunzhao again. So I completely agree with your point, but actually what happened to the mepo program, that they did study three doses in the dose-ranging study for exacerbation, and there's no dose response observed. That is definitely true. And based on that, they go to choose the lower dose, not the higher dose.

DR. OWNBY: Okay. I've got Dr. Morrato and Dr. Cook in that order.

DR. MORRATO: Mine's a quick one, I think. I wanted to follow to what Dr. Voynow had asked earlier, which in the study that had the eosinophilic esophagitis, it was estimated maybe about 80 to 90 other adolescents were at the 3 milligram dose.

Did FDA pull out that safety data, or should

we put any weight to it? Or should we really just rely on the N of 19 that was in the control trials?

DR. DONOHUE: I focused my safety analysis on the asthma cohort. I did not include events from the earlier studies.

DR. MORRATO: Should we consider that as we weigh the safety? The sponsor is saying they have data up to 250 kids, so what's the FDA's view on that as they look at the safety package?

DR. KARIMI-SHAH: This is Banu Karimi-Shah from FDA. I think that that data from the sponsor is supportive, but again, we have the data that we have for adolescents. We do have data in the proposed population, so I think that data carries more weight. I think the data in the eosinophilic esophagitis children can be supportive to that data but cannot take the place of that data.

DR. MORRATO: Is the profile similar in the other group? I mean, because right now, we're asked to make an assessment off of 19 children that took the medicine.

DR. KARIMI-SHAH: This is Banu Karimi-Shah

again. I would ask the sponsor if they have that safety data separated out for the eosinophilic esophagitis adolescents, if that would be helpful for you. We don't have that separated out.

DR. MORRATO: Does the sponsor?

DR. SHAH: Absolutely. May we have Dr. Shalit review that data, please?

DR. SHALIT: Slide up, please. So this is a very busy slide, but this summarized both the placebo-controlled asthma studies as well as those of esophagitis. For the convenience of the reviewer, we summed the 1 to 3 milligrams in the esophagitis study together.

As you can see, the AE profile was very assuring and similar in both asthma and the esophagitis study. We also have this data but by dose for the esophagitis study, if you're interested to see it.

DR. MORRATO: Yes, please, because we're hypothesizing that dose might make a difference.

DR. SHALIT: Slide up, please. So once again, the placebo-controlled esophagitis study by

dose, we didn't see any dose-related adversity.

DR. MORRATO: I'm looking at the anaphylaxis, because those cases were just in the controlled study; is that --

DR. SHALIT: Yes, these are only in the controlled, two in reslizumab and one in placebo, and it doesn't include the data from the open label study

DR. MORRATO: Thank you.

DR. OWNBY: Dr. Cook.

DR. COOK: Jack Cook. So without a lecture of why I think models -- anything you do is full of assumptions, what you observed. I'd like to actually hear from the sponsor. We do note a difference in the observed effect from that study for 0.3 milligram dose and what the model predicts, and there's about a tenfold difference.

If you could come up to why you think the model is qualified, that may help avert some of the arguments we have or discussion we have.

DR. SHAH: So let me have Ms. Bond respond to that question.

MS. BOND: So there are a number of reasons why we feel like although directionally similar, the results of the individual study versus the model might be numerically different. And that would be, first of all, with 3081, you're looking at a single study. With the model, we are looking at pooled data across the entire program. And as discussed before, all of the qualifications we had for those data to make it into that model.

There are different types of approaches, so with the individual study, we have values that are -- it's a mixed model, repeated measures. Those are values closer to a mean, whereas with our model data, our pooled data, we are talking about a nonlinear mixed effects model will give you values closer to a median.

For the individual study, dose was used. For the pooled database, as referenced earlier, we're looking at an exposure response model. So there's a number of differences between them in methodology that could contribute to those numerical differences.

DR. COOK: So you think that that's the reason for the tenfold difference in the estimated effect?

MS. BOND: We believe that those are a number of the reasons that contribute, probably among others in terms of methodology.

DR. SHAH: And just to add again, in the earlier studies when we looked at 0.3 milligrams, we saw no effect at that earlier study in the people with elevated eosinophils. That's why in the model if we're to take all the data, the effect size is also reduced because of that.

DR. COOK: Right, right. So when you saw that, you saw an effect of zero, or you saw no statistically significant effect? Because there's a difference between the estimated effect -- and that sometimes has to do with sample size -- and a statistically significant effect.

DR. SHAH: No. I'm talking about treatment effect in the context of --

DR. COOK: So it was zero?

DR. SHAH: Yes, there was no effect in that

study at that dose.

I think Dr. Adkinson has one more comment to add, please.

DR. ADKINSON: Since the dose discussion also has to do about safety, I just wanted to respond to a suggestion that was made over here this morning that a lower dose is going to be associated with an expected lower rate of allergic reactions or anaphylaxis. But of the three cases of anaphylaxis seen with the 3 milligram dose, two of them occurred during the infusion, suggesting a much smaller dose would probably have produced the same clinical reaction.

So the dose-response curve for anaphylaxis in immunologically-mediated doses doesn't necessarily go down with reduced dose in a way that's clinically meaningful.

DR. OWNBY: I have a couple more questions coming. Ms. Holka.

MS. HOLKA: Yes. Thank you. This could be very obvious to everyone else in the room, but I am not a physician. So my question is, we're looking

at a proposed indication for severe asthma, but you've studied relatively a nice size group of people with EoE. So I'm wondering why are you not looking also for that indication.

DR. SHAH: The EoE studies were successful in showing a reduction in tissue eosinophilia and blood eosinophilia, but there's not an agreed and approved patient-reported outcome that has been shown to be sensitive and showing a benefit of therapy in that disease state. So the clinical trials could not show a symptomatic improvement of the patient's EoE symptoms, and so the program was stopped because of those reasons for the EoE indication.

DR. OWNBY: Dr. Voynow?

DR. VOYNOW: This is a question for the FDA. There were a few centers that were sites that were closed because of violations in their practice. Is it valid, though, or should we be considering any adverse events, and particularly the two that we're most worried about or that have been raised, anaphylaxis and musculoskeletal, from those sites?

I just don't remember us discussing that.

DR. DONOHUE: This is Katie Donohue with the FDA. The usual definition for a safety population is any patient randomized to at least one dose. In this case, there were a few sites that had pretty significant GCP violations, so the sponsor dropped the sites and excluded the data for those patients from both safety and efficacy analyses.

I raised that one case because I thought it was pertinent to one of our safety signals.

DR. SHAH: Can I just make a comment on that, please? Because Dr. Shalit could actually cover the cases because there was not -- I don't think we provided complete information on that case that was mentioned.

Dr. Shalit.

DR. SHALIT: I just want to note that the data of these studies was provided, part of the CSRs, the clinical summary reports. It wasn't included in the table of summaries, but it was included in listing.

One of the cases that was brought up by the

FDA was a possible rhabdomyolysis case, which is detailed in the addendum that we provided you. And our assessment is that this case doesn't follow the definition of rhabdomyolysis. Just of note, it was a patient with a previous shoulder pain on the day of the infusion before. Then the drug was administrated, the CPK was elevated to 1500, and it was only a single elevation accompanied by muscle pain, which resulted while on treatment with normalizing of CPK values. So just of note.

DR. VOYNOW: This is Judy Voynow again. So just to follow up again then to Teva, I guess a larger question would be, would adverse events within the centers that were stopped, would that affect your total analysis then or your summary with respect with that increase of possible adverse events in the treatment group versus the placebo?

DR. SHAH: So maybe I can have Dr. Shalit answer that question as well.

DR. SHALIT: No, it didn't. I can provide you -- to make things clear and short, slide up, please. So this slide, it's one of two. It

summarized all the AEs in these two sites. And as you can see, these are common reported AEs.

Can you move to the next slide, please? And the case at the below row of urticaria, this was a case of a patient who developed urticaria 9 days after the infusion. We don't think it influences our assessment of anaphylaxis risk.

DR. OWNBY: Are there any further -- well, Dr. Yu, you had a question. Excuse me.

DR. YU: Thank you.

I just have a question. I'm still puzzling about this dose variation versus the change in FEV1. I know in FDA's background documentation, it shows the figure 1 on page 13. It shows a diagram of a mean change from baseline, FEV1 to changeover 16 waves, and it compares change in baseline FEV1 amount, placebo, dose 0.3 and 3 milligram.

But the sponsor did not show this diagram. Instead, they showed the model change. Because there's no error bars or confidence bars, the previous question. So I really couldn't tell how reliable this modeled dose variation versus change

effect on the FEV1 in comparison and showed by the FDA.

Do we interpret -- in the figure 1, I got -- if I'm understanding correctly, both doses show effective, improve the breathing, but the difference between 0.3 and 3 milligram are not significantly different. But when you look at the model, are we supposed to look at them also not significantly different?

I'm just a little -- do I understand the -- did I --

DR. KARIMI-SHAH: So this is Banu Karimi-Shah from FDA. So you're correct. So in figure 1 in our briefing documents, that figure which you're referring to is from study 3081, and that shows actual data with point estimates and confidence intervals surrounding those point estimates from mean change and lung function from baseline at various time points, from baseline, 4 weeks, 8 weeks, 12 weeks, and 16 weeks.

This is the actual data from the study. And you're correct in saying that there was no

difference between the response to the two doses because the confidence intervals were overlapping.

I can't speak to the sponsor's model because I think that's what Dr. Brittain was asking as well, is sort of the error around those point estimates. But this is the actual data from study 3081, which shows no difference between 0.3 and 3 milligrams per kilogram with respect to lung function.

DR. YU: Thank you.

DR. OWNBY: Dr. Tracy, you had a question?

DR. TRACY: Thank you. This goes back to the sponsor. We may have actually covered this, and if so, I apologize. Going back to the CPK elevations, do we know how fast it came down?

DR. SHAH: I'm sorry. How fast the --

DR. TRACY: Yes, I'm assuming you did some follow-up surveillance.

DR. SHAH: In terms of the -- I'm sorry. I'm not quite sure I'm understanding the question.

DR. TRACY: So I'm assuming you drew your enzyme level because of musculoskeletal concerns.

DR. SHAH: No, this was a routine chemistry part of the safety monitoring we were doing in the program. So we collected it right before ever infusion.

DR. TRACY: So let's say you just found one that's markedly elevated, and some of those are pretty elevated, recognizing that they were also asymptomatic. Did you see how quickly it came down?

DR. SHAH: In most cases, it was shown even by I think Dr. Donohue's slide, those cases that were elevated. In almost every one of them I believe she showed resolved with continued therapy in the next one to two time points, which would have been one to two months.

DR. TRACY: And I'm also clear that we really don't know why it happened yet; is that --

DR. SHAH: No. But as I explained, the CPK elevations can occur for many reasons. And we had one individual who was weightlifting very aggressively and had extremely high CPK value. He came into the clinic for his infusion right after

he had done weightlifting. And it's been reported by many in the literature about weightlifting and any physical heavy exertion can have significant CPK elevations associated with that.

DR. TRACY: Thank you.

DR. SHAH: And just to be clear, there were these same high values seen in placebo as well.

DR. OWNBY: Okay. Any further comments before the committee receives their charge? Dr. Dykewicz?

DR. DYKEWICZ: Dr. Dykewicz. Clarification on the CPK point in terms of the rapidity of the resolution of the elevated CPK. You did present case 123 that had some graphs. But I think speaking to the question about how rapidly the resolution or improvement occurred, I wasn't clear about the time axis because of the size of it. So if you could maybe readdress that question on the basis of the data you have.

DR. DONOHUE: My understanding is that most of the values were drawn the following month. The frequency of checks for CPK were -- for the

protocol, the most frequent interval was a month. There were a few that were further out. And Teva can speak for individual patients if closer monitoring were done for elevated values.

DR. SHAH: Right. So I think clearly, once we see that someone has a high value, the physician and we want to confirm that it's not remaining high. For those individuals who did have those very high values, there would have been in many of those instances follow-ups that occur within the week once they were identified as being high on the routine blood test. And in those cases -- can you please come up?

DR. SHALIT: For example, the second case in the presentation, it was a week after. The investigator received the results. He invited the patient to be retested.

DR. OWNBY: Dr. Georas?

DR. GEORAS: This goes back to the question of dose, and I can see that there's no statistically significant difference between 0.3 and 3 when it comes to FEV1 based on the data

presented in figure 1 or CE-15. But if you look at that together with the eosinophil reduction numbers, I think it also seems to me that 0.3 is not at the plateau of the dose-response curve. And maybe there's a dose between 0.3 and 3 that would have plateaued like 1 milligram per kg or something like that, but we don't know.

But we have a pretty rich data, it would seem to me, now between multiple studies about the reduction of eosinophil blood counts. Is it possible to use that as a model to predict efficacy and exacerbation reduction, for example? Because looking at the reduction in eosinophils with 0.3 versus 3, it's clear you don't quite get the same. I'm just wondering if there's any data there.

DR. REN: So I don't have the slides here. I'm very happy you raised this question, which the eosinophil count, the PD marker, put that PD marker together with efficacy in this context.

So yes, in terms of this reduction of eosinophil count, we see a significant more decrease in higher dose, 3 milligram per kilo, than

the lower dose, 0.3 milligram per kilo. That's a piece of supporting evidence to choose the high dose.

From mepolizumab program, the reason they choose the lower dose is because the lower dose is almost as effective as the high dose in terms of this reduction magnitude.

So does that answer your question?

Come back to the final question, if in terms of using this absolute number, the relationship between this absolute eosinophil count and reduction, let's say FEV1 change, we did some very preliminary analysis, and we see the trend in terms of this trend is more clearer when you use the difference, the change from the baseline of the eosinophil count in terms of the absolute number. But that's just very preliminary analysis.

So it could be that if you use the delta change of the eosinophil count versus the FEV1 change, it could be a better prediction.

DR. OWNBY: Dr. Castro?

DR. CASTRO: Mario Castro. As a disclosure,

I was an investigator on the SIRIUS study for GSK on mepolizumab and have been very interested in all the anti-IL-5 therapies in comparing these subtle differences between the three agents.

I think from the mepolizumab data, it's clear that there is a dose relationship when we look at airway eosinophilia. Clearly, at all three doses, it reduced blood eosinophils. But when you looked at especially the DREAM study, the largest study, where they looked at sputum eosinophils, the lowest dose was not statistically significant in reducing airway eosinophilia.

So as a clinician, I worry if you don't reduce airway eosinophilia, does that explain the variability in the lung function improvement that we saw with mepolizumab? So I bring that up as a concern. I understand that we still want to go with the lowest dose that efficacious, but I'm also concerned that if you don't reduce airway eosinophilia, that you're not going to get the same improvement in lung function that we see with the 3 milligram per kilogram dose.

I think that's why there's consistent -- at the weight-based dose of 3 milligrams per kilogram with reslizumab, there's consistency in terms of improvement in FEV1.

DR. OWNBY: Dr. Chowdhury?

DR. CHOWDHURY: Maybe I would like to answer the question that was raised regarding eosinophils and exacerbations on efficacy measures. I think conceptually with the class of drug being studied more recently, it is understood that eosinophil has something to do with lung functions and exacerbations and is a beneficial response to drugs blocking this.

But specifically, I don't think we have a number, at least in the blood eosinophils, what level of reduction is necessary to achieve a benefit. So that is really not there. And if you see at the 0.3 and 3, 0.3 actually also reduces eosinophil count in the circulation by close to 70 percent. Of course, 3 did much higher than that.

Also, you have to keep in the context, this

drug is really for reducing exacerbation, not for reducing blood eosinophil count. If that was really the measure that you were going to target against, then it would probably dose to the eosinophil number, and that would be individualized by patients. Here, we're actually talking about a mean.

To bring it to some relevance with another biologic a long time ago, which was studied, approved, is the anti-IgE molecule that was actually targeted to the IgE level. So everybody actually had a different dose, but target was IgE level. So that was entirely different where you target the 2-A level. Here, you're actually dealing with a mean.

So it is quite different. And actually when you look at the anti-IgE molecule when it was studied in the chronic urticaria, the link with IgE is questionable. It was actually studied at a fixed dose, and there were three doses studied, which actually all worked.

So the longwinded answer to your question is

we do not really know what level of reduction of the count in blood is necessary for efficacy. It is entirely possible we need 90 percent. It is entirely possible something lower would also do it. We do not know.

DR. SHAH: I think that is a fair point that it is hard to always show these relationships between biomarkers and clinical effect, but we actually did look at the relationship between lung function improvement and exacerbation reduction risk in the two exacerbation studies.

I don't know. Maybe Dr. Zangrilli can just quickly summarize those findings. They may help the question of is lung function useful to assess exacerbation risk, which I think some of the panel is raising.

DR. ZANGRILLI: Sure. Realizing this is extending the doctor's question from eosinophils to FEV1 to exacerbations, I do believe what Dr. Castro said; you do need robust eosinophil reduction in the lungs to achieve an effect.

(Pause.)

DR. ZANGRILLI: Sorry about the wait. I didn't necessarily intend to present this because as your data is, this is rather preliminary as well, but if you put the slide up.

If you believe that higher doses of reslizumab produce more effect, which we have shown with the model -- which I realize is controversial. I realize it's debatable. We just, a priori, suggested that a 100 mL change in FEV1 is something patients can feel. It's clinically significant.

So patients that respond with 100 mL change enjoyed a very substantial reduction in FEV1. Folks that did not, patients that did not have a 100 mL change had a lesser effect.

This is, I realize, an indirect answer to your question.

DR. GEORAS: Could you show [inaudible - off mic.]?

DR. ZANGRILLI: I apologize. Let me take you through it because there is more detail. So the endpoint we chose -- we said change in FEV1 at week 16. So early improvement in FEV1 relates to

future risk. So that was the hypothesis.

So we looked at change in FEV1 and at 16 weeks, and we suggested that a change in FEV1 that was a response is a 100 mLs. And if you achieve that response, that subgroup of patients had a 71 percent reduction in exacerbations. Four weeks, 8 weeks, 12 weeks, our other FEV1 levels are still very much being looked at, so sorry about that.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: Can I just ask a question? What were the Ns for the two groups, and what was the variance?

DR. ZANGRILLI: Are the Ns on the table? Can you put the table back up again, please? I apologize.

So you're asking about the Ns for the subgroups. I'd have to get that for you, Dr. Morrato, and the variants. We do have that, but I'd have to follow up on that.

DR. OWNBY: Okay. If there are no further clarifying questions, we'll move on to the charge to the committee, Dr. Karimi-Shah.

Charge to the Committee

DR. KARIMI-SHAH: In the next few minutes, I'd just like to present our charge to the committee. These were the issues that we had flagged earlier in the day for consideration of which we've enjoyed a lively discussion, so thank you very much for all of your comments.

Just to review briefly, the first bullet here talks about the adequacy of dose ranging and dose selection. I think we've had a very lively discussion, and we look forward to more discussion as we get into the questions today.

I think what I'd like to summarize here from the agency's perspective is that while modeling has its place in a lot of arenas, we know from the study results of 3081 that two doses were studied and both doses showed efficacy of an FEV1 change greater than 100 mLs. The sponsor does cite that the dose was selected based on the maximal reduction in eosinophils, but we don't know what that reduction should be in order to achieve clinical efficacy.

Point number 2 here is the adequacy of the safety evaluation with respect to both anaphylaxis and muscle toxicity. And the discussion was also raised today about malignancy, so we appreciate that, and we look forward to your discussion on that as you discuss the safety today.

Finally, the risk-benefit assessment in patients 12 to 17 years of age.

So here is the Code of Federal Regulations standard for the approval of an application, and here it states that "FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing controls, and labeling."

For the purposes of today's advisory committee discussion, we ask that you focus your discussion on the standards for safety and efficacy. Manufacturing controls and labeling should not be the focus of today's discussion.

Here's the efficacy standard again -- I had displayed this earlier this morning -- stating that

substantial evidence consisting of adequate and well-controlled investigations are required, that the drug product will have the effect it purports or is represented to have.

We have typically taken this to mean that the dose selected and efficacy shown for the dose selected as it was carried forward in the clinical development program should be scientifically justified and have an adequate efficacy and also safety profile.

So leading into the safety standard here -- I've also flashed this earlier today so I won't go through this in great detail. But again, this is a safety standard that is used to decide whether an application should be approved. So if the application did not include adequate tests, or the results of these tests did show that the drug is unsafe, or there was simply insufficient information to determine whether the product was safe would all be grounds to not approve an application.

We have a total of five questions for you

today. Two of these are discussion items on efficacy and safety, and there are three voting questions. And I will go through each of these questions and read them carefully here, and then we can move on to the discussion and voting.

So question 1 is a discussion question. It asks that you discuss the efficacy data for reslizumab 3 milligrams per kilogram IV administered once every 4 weeks to support its use in the treatment of asthma. We ask that you consider the following issues in the discussion: A, the adequacy of the dose-ranging data; B, the adequacy of efficacy data in children 12 to 17 years of age; C, the adequacy of the data in the U.S. population; and D, the role of blood eosinophil counts in determining the target patient population.

Question 2 is a voting question. Do the efficacy data provide substantial evidence of a clinically meaningful benefit of reslizumab 3 milligrams per kilogram IV once every 4 weeks for the treatment of asthma in adults 18 years of age

and older and in children 12 to 17 years of age? If you were to vote no, we do ask that you provide comment and provide discussion on to what further data should be obtained in both of these cases.

Question number 3 is a discussion question. We ask that you discuss the safety data for reslizumab 3 milligram per kilogram IV with specific consideration of the findings of anaphylaxis and muscle toxicity. Again, you also raised the question of malignancy, so we appreciate that discussion as well.

We ask that you comment on the potential impact of additional dose-ranging data or product attributes when discussing the anaphylaxis safety signal and safety signals in general.

Question 4 is a voting question. Is the safety profile of reslizumab 3 milligrams per kilogram IV administered once every 4 weeks adequate to support approval for patients with asthma? If you vote no, what further data should be obtained? Please also include in your discussion if you do vote to approve but would like

further data postmarketing, we would appreciate that discussion as well.

Question 5 is a voting question. Do the available efficacy and safety data support approval of reslizumab 3 milligram per kilogram IV every 4 weeks for the treatment of patients with asthma? The question about approval is again broken down by age group in adults and then in children 12 to 17 years of age with a further discussion question if you do vote no, to what further data should be obtained in both scenarios.

Thank you very much. I'll turn the meeting back to Dr. Ownby now for the discussion.

Questions to the Committee and Discussion

DR. OWNBY: We will now proceed with the questions to the committee and the panel discussions. I'd like to remind public observers that while this meeting is open to the public for public observation, public attendees may not participate except at the specific request of the panel.

So we are back to the question 1, which is a

discussion question. Are there any questions from the panel first about wording or minor issues that we can solve, or should we move directly into the overall discussion that's requested?

I don't see any concerns about the wording, so we need to discuss the efficacy data presented for reslizumab 3 milligrams per kilo IV administered once every 4 weeks to supports its use in the treatment of asthma with the four considerations listed.

Does anyone in the panel want to comment on that, or are you all questioned out?

(Laughter.)

DR. OWNBY: I can't believe it. Dr. Platts-Mills and then Dr. Brittain.

DR. PLATTS-MILLS: I think the thing that I would like to see is a real analysis of the blood eosinophil count means, that is that there are lots of reasons for getting eosinophil counts. Helminth is an obvious one, but we think that the population studied, that's not relevant. But sinus disease is obviously another one.

Clearly, I'm not saying that -- these are not criticisms of where we are. They are things that I think need to be studied once this is -- if this is in use. That is, sinus disease, fungal infection, fungal infection elsewhere.

We're left at a very odd situation of the patient who is enrolled who had lung tuberculosis and died of lung tuberculosis. That clearly is a signal that good evaluation of a chest x-ray should be part of any decision to put someone on the drug.

But yes, I think the key thing -- and also, in the population under 17, are these actually just allergic patients who are highly allergic and highly exposed and eosinophilic because of that, and knocking out their eosinophils will not deal with the situation, and that the really poor result in the group under 17 is real. If so, it's a very interesting message indeed. That should clearly be investigated further.

DR. OWNBY: Dr. Brittain.

DR. BRITTAIN: I guess I have a couple comments. I'm not sure whether I want to

say -- and if it goes back to A, whether the dose-ranging data are inadequate or adequate. But it's clearly unfortunate that there's not more information about exacerbations at different doses.

We have the FEV1 studies with 0.3 and 3, and that's a tenfold difference. We don't have the exacerbation data like we would ideally want to have.

I'm a little uneasy about the pediatric data. There's not much of it, obviously. In terms of -- so I mean, maybe you could say that there would be -- it's hard to imagine that it would be different from the overall population, but the limited amount of data we have is all a big negative.

It does make me a little concerned that maybe there's something there, and it's certainly not enough to say that we know what's happening in that younger group.

DR. OWNBY: Dr. Weber.

DR. WEBER: A couple of things, I certainly concur that the dose-ranging data is less than

exciting, that certainly more data points would have been nice with other doses.

Addressing the second point, again, the data on the efficacy in the adolescent range is again less than compelling. It raises an interesting point that I think that Tom just kind of alluded to, and that is perhaps in younger age group, inhalant allergy may play a larger role in their disease, and that perhaps what the message here is, is that we need to pay attention to what's driving the eosinophil and not the eosinophil count by itself.

I have another point to make, and I don't know whether to enter it here or not. But since I've got the floor at the moment, I'll go ahead and do that.

The one graph that I think is slide number 12, the subgroups looking at different levels of eosinophils and then the response to the FEV1 certainly suggests that there is threshold phenomenon that we may be peeing in the ocean -- that's probably not the appropriate

analogy to use in this forum.

(Laughter.)

DR. OWNBY: It has been recorded. You're okay.

DR. WEBER: Yes, well, let me reinforce that this is Richard Weber speaking.

(Laughter.)

DR. WEBER: Anyway, it sounds like the drug itself may be less than eventful with lower levels of eosinophils, and I think that is a point that we need to discuss as to what the indications for at least the suggested patient levels are for the use of this drug; although knowing that once an agent's on the market, you can use it for whoever you want for whatever you want as long as you can defend yourself in court. Thank you.

DR. OWNBY: Dr. Yu and then Dr. Greenberger.

DR. YU: Thank you. I have a question about the instruction on the standard, safety standard guidance from CFR. And on those guidance, there's one for refusal to approve an application. There are three listed criteria.

Are we supposed to use all three of them, or can either one of them would be justified for refusal?

DR. KARIMI-SHAH: So you consider all three, but any of those could be grounds, any one of those three, so don't have to have all three satisfied in order to refuse to approve it.

Does that answer your question?

DR. YU: Yes. Thank you. My other comments I have, as a patient and consumer, when you go to a doctor's office, you don't really feel the blood count, ES count. What a patient mostly feel is how I feel. If I have more exacerbation, I go to hospital more often.

So that's just the parameters that seems that common people can more relate. But unfortunately, it's really unfortunate that we don't see dose-range trials, exacerbations rates on 0.3 or any variation dose that could be more -- give guidance for the consumers, also.

Thank you. Those are my comments.

DR. OWNBY: Dr. Greenberger.

DR. GREENBERGER: This has to do with, A, the adequacy of the dose-ranging data. I think we have enough information to vote, and I come from a background of advocating from the terms and the thoughts behind using endotypes of asthma. So I'm happy to see that this information today is informative to healthcare professionals and MDs who can see that in steps 4, 5 and 6 asthma with EOs over 400, there's a possible therapy.

To follow up what I asked about the difference between the median and the mean, from what the company said, it would appear as if there's an advantage to using this medicine because some people in more than controls are going to have no exacerbations, which would suggest that more than half the people are going to be better than normal responders, so to speak. So that's beneficial, the way I interpret the information.

DR. OWNBY: Dr. Morrato and then Dr. Georas.

DR. MORRATO: Thank you. This is Elaine Morrato. I wanted to comment on the adequacy of the efficacy data in children and the eosinophil

count as well. If I'm using a standard that the FDA shared, which is substantial evidence, I just can't in good faith say 19 children is substantial evidence. I know from a regulatory sense, you may decide to approve in kids. It's what was done before for mepolizumab. But I feel 19 is not much more than a qualitative data study, and we don't approve drugs based on qualitative data in case series.

So based on that, that's how I was viewing the information. And from the standpoint of the N, it's also problematic that the data that we do have is not consistent and it's often pointing in the wrong direction favoring placebo, not the drug.

With regard to the question around the role of eosinophil, I would agree with, I think, what Dr. Platts-Mills and Weber were saying, that more information is there or needed.

I'm anticipating that if this follows a similar labeling as the prior drug -- and I don't disagree with the notion of the eosinophil phenotype as the labeling and the approach, and

then in the clinical studies section, you say here's the counts that were used and how it was determined -- that care needs to be done in how that's reflected in the labeling for this product.

Maybe that's what you were hoping we would discuss, because I think it should reflect what was actually tested, not necessarily what was the eligibility criteria.

So if the clinical population is predominantly 600 to 700 range, then that needs to be what gets communicated. So as providers, as patients are making decisions on is this a drug right for them, people understand what was the type of patients that were in these trials.

I know a lot of the slides that were presented by the sponsor used 400 as their cut point. That's a nice consistent number that fits with the population-based study that was quoted, but I would like to see not just the 400 point but beyond the 400 point and is there really a threshold that's happening at 600 at their data. They did a lot of work looking at the lower number,

not so much the upper.

I'm anticipating that -- and I may be wrong -- that this might be an area of market differentiation and claims. And therefore, I think it's important that clinicians and patients are informed to, as I said, the types of patients that were in these studies.

DR. OWNBY: Dr. Georas?

DR. GEORAS: Yes, at this stage, I guess I'm trying to step back and take a 10,000-view after we've been talking about some very important details. As a practicing asthma clinician, I would echo Dr. Greenberger's statement that I think this compound does address an unmet need and it's in severe asthma. And the reduction in exacerbations and symptom improvement at the 3 milligram dose, I find compelling.

But I would also second the comments of other committee members that I think the company could have done a better job in addressing the dose-ranging data, as has been brought up today. It seems that 0.3 is not enough, but whether 3 is

too much or not, unfortunately, at this point, it's going to be a matter of our all interpreting the data and almost speculating.

I also would second the idea that I think we're being put into a very difficult position to address the efficacy and safety in the adolescent age group with such small numbers. You're asking for a discussion, but we all see the same data. And I think it's just very, very hard to give you concrete guidance, at least in my opinion.

The thing I'm struggling the most with is D, because I know we're being asked to think about an eosinophil phenotype. And it's clear that stratification and endotypes are important, yet we heard from the statisticians that there's no relationship between eosinophil count and change in lung function, right?

So I think that's also a kind of challenging place to be at this point. I guess it's ultimately an agency decision, and that's more perhaps in the product labeling and wording. But I think there's -- so you want us to discuss the eosinophil

phenotype, but we can't really use blood eosinophils, which is what we have to go with. So it kind of puts again in a little bit of a bind, Dr. Chowdhury.

DR. OWNBY: Dr. Stoller?

DR. STOLLER: I'll reflect on two points, one in particular and one more general. With regard to question C, the adequacy of the efficacy data, I would echo the comments made before. I think that if one were looking for a specific indication in adolescent groups, one would imagine doing a trial that specifically recruited for that population. And given a total of 25 children on the efficacy side and fewer on the safety side, it's very hard for me to answer affirmatively that we have adequate data in children to speak to the efficacy or safety of this drug. And I think my votes later will reflect that.

On a broader context, just reflecting on my general experience and service in this group, I find myself in this conversation having to impute data much more frequently than is normally the case

with regard to dose and efficacy and safety.

Now to put a finer point on that issue, on the efficacy side, I think there's little doubt, with regard to the primary endpoint of exacerbations in 082 and 083 at 3 milligrams per kilogram, that there's a strong signal that addresses an unmet need that my colleagues have stated.

I think of the issue of dose response as being more germane on the safety side. That is to say, what one would like to do is to look at the smallest necessary dose. This has been done in other studies on ICSs and conversations I've been involved in, in this forum.

So the issue of dose ranging, in my mind, is less impactful on the primary outcome measure of exacerbation frequency, where I'm quite satisfied that 3 milligrams per kilogram is impactful. But on the safety side, the question is which of the safety effects do we know enough about to say that they are potentially dose dependent?

As was pointed out and I agree with, the

anaphylaxis risk in general is not considered to be a dose-response effect as immunologic reaction. So I'm less concerned about that.

I am a bit more concerned about the CPK issues with regards to essentially no data on dose impact and in fact no data on the pharmaco -- on the change of CPK over the time frame in which we think CPK is normally cleared. So I have to sub-segment my response to the dose response question by indexing it to the specific side effect that we're looking for.

Just again to be clear, I'm not concerned at all about the dose-response effect on anaphylaxis, but I think there are major questions related to my imputing comment before on the CPK issue. And to the extent to which CPK -- admittedly, there are very few clinical events that doctors would identify as associated with renal failure and hematuria and the full blown rhabdomyolysis that we worry about. If there's a concern, as there were in statins, that this is the tip of an iceberg, I think that's an unanswerable question based on the

data that we have.

DR. OWNBY: I'm a little surprised at the committee. I was looking back -- this is the FDA briefing slides on page 3. There are two things that stand out. One, there's no efficacy data in the U.S. population. But more specifically, we've talked about the adolescents which worry me, but also, the African Americans, there's no efficacy. I mean, it comes up null and actually a slight exacerbation favoring placebo.

Knowing that this will be used in all racial groups, I find that very concerning because in my experience as a clinician is that African American patients are not always, quote, "the same" as other groups that I see in the way they respond to medications, and it bothers me we don't have better information there.

Dr. Dykewicz, Dr. Cook, and Dr. Morrato.

DR. DYKEWICZ: If I might just second, I guess, a concern. One of the things FDA did ask us to look at was the adequacy of the data in the U.S. population. And if you look at the two key trials,

82 and 83, you're looking at a situation when you split out the U.S.A. population where you are not demonstrating a clear reduction in exacerbation rate.

I don't know how to explain that. It's difficult to dismiss. There was benefit in terms of FEV1, at least in terms of study 81. But this is problematic.

DR. OWNBY: Dr. Cook?

DR. COOK: Just a couple of comments. I'm glad the U.S.A. was brought up because that's the one I wondered why we had so much concern about pediatrics.

But in the absence of any data, would we feel comfortable extrapolating to that population? That goes back to your comment. I don't know why I would expect them to be different, although I did hear for the black, that you might expect or at least there was some idea that they might not behave the same. But that's one thing I think we ought to discuss, is why one would expect those to be different in order to extrapolate where we don't

have data.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: Well, one hypothesis might be that you have different background clinical care going on, and therefore, the types of patients that are being enrolled in the study, while meeting on paper the eligibility criteria, may have different history of disease coming into the trial and/or other forms of supportive care that's different. So what we're seeing is maybe an interaction due to that.

DR. OWNBY: Dr. Greenberger?

DR. GREENBERGER: This continues what Dr. Dykewicz was talking about, but I think regarding the U.S. data, the study wasn't set up to test the response of this treatment of people in the U.S. versus elsewhere; is that correct? But within the world of severe asthma, there's eosinophilic severe asthma. There's eosinophilic plus neutrophilic on biopsy severe asthma, and then there's like neutrophilic type, and then there's possibly granular type.

So this may have identified people whose EOs go down, whose FEV1 goes up, but the exacerbations are not impacted by this product. So it could be just identifying maybe a different subset of these people with severe eosinophilic asthma.

DR. OWNBY: It concerns me that these are all possibilities, both Dr. Greenberger's and Dr. Morrato's comments, as to why we're not seeing the same robust signal in the U.S. data set. Admittedly, it's smaller, but I'm assuming we're only approving this for the United States in terms of the discussion and not for the world.

Dr. Cook?

DR. COOK: Just to comment, one can take the data in hand and make some assumptions about efficacy, and then would the Ns that you have for these small groups, what is the likelihood that you would get a result at that? So you're kind of right at that -- sometimes that helps you make a decision if you find that in X percent of your trials -- if you have a high enough chance of seeing like that, I might be more inclined to say

that's a anomaly because of the small N rather than that being a truly rare occurrence or something being able to happen that way.

So just suggestion of all the great things you get to look at because we don't have any of that data here to dig down in.

DR. OWNBY: Dr. Morrato>

DR. MORRATO: I also wonder if black here is defined as African American black, or is it defined as -- were their African sites, or other countries in -- so how much -- so the black line may actually be very linked with the U.S. site information as opposed to being something unique in African Americans.

So is the majority in that subgroup really African Americans? Can I --

MS. ZENG: Yes, this is Lan Zeng. The definition of black, I think the sponsor will provide more specific information, but I do have the data in terms of the number of black subjects who are actually U.S. patients.

In study 3082, there were a total of

34 black patients. Fifteen of them, which is 44 percent, resides in U.S. In study 3083, there were 10 black patients. Eight of them, that's 80 percent, resides in U.S.

So the not so favorable treatment benefit you observed in 3083 is driven by patients residing in U.S.

DR. MORRATO: Right. So it could be access to care. Because exacerbation included -- I mean, I go to hospital for my -- I have an attack, right? So if there's variation -- did you see -- was there variation in what was triggering the endpoint in that group? Was it an access to care issue? You know what I'm saying? Yes. But you can't tell because we don't have the information.

DR. OWNBY: Other comments or questions about this discussion point before we move on?

DR. GEORAS: Could I ask just a clarification from the group? Maybe I'm missing it now. For the U.S. population, there is evidence for FEV1 effect, right? Yes.

Okay. So there's FEV1 effect but not an

exacerbation effect. So I mean, in my mind, I think it's possible that something like what you're describing, Dr. Greenberger, is going on. But it's also possible that this is a statistical fluke driven by small numbers. It's hard to come up with a rationale why you would see the eosinophil effect, the lung effect, and then have an enhanced exacerbation frequency. That's just very hard to think of in a biological way, for me at least.

DR. OWNBY: Dr. Karimi-Shah?

DR. KARIMI-SHAH: Yes. Hi. This is Banu Karimi-Shah from FDA. So to Dr. Georas' point as well, so study 3084 was the 16-week lung function study, and that was done entirely in the United States. So all of those patients were in the United States. And when the FEV1 is looked at across the eosinophil counts, so not broken up into thresholds and quartiles, that study did not show an FEV1 effect.

DR. OWNBY: Any further questions before we move on to question 2?

(No response.)

DR. OWNBY: Seeing none, question 2 is the voting question. Do the efficacy data provide substantial evidence of a clinically meaningful benefit of reslizumab 3 milligrams per kilo IV once every 4 weeks for the treatment of asthma in adults 18 years of age and older and in children 12 to 17 years of age?

Would you like to discuss the question before we vote? Dr. Tracy.

DR. TRACY: It almost seems like they're really answering two different questions here.

DR. PLATTS-MILLS: There are two separate questions.

DR. OWNBY: As I understand it, we're going to vote as two separate questions on this? Yes, so we'll be voting two separate questions.

Any other questions, or are we ready to vote?

Dr. Yu?

DR. YU: Oh, I just want to make a comment. The anaphylaxis signal, true, from whatever the data present to us, the numbers are small. But if

you think about when the drug is marketed and put out for lots of people to use it, in reality the population will be different from when you're selected for doing the trials. And you have more people who probably have unknown risk to anaphylaxis. So this signal of anaphylaxis, I just do not think, as many colleagues here alluded, that cannot be ignored. That's a consumer's perspective.

DR. OWNBY: Dr. Morrato, you have a comment?

DR. MORRATO: We're just voting on efficacy at this stage, am I correct?

DR. KARIMI-SHAH: Correct.

DR. OWNBY: Any further clarifications?

(No response.)

DR. OWNBY: Okay. If there's no further discussion on this question, we'll begin the voting process. Please press the button on your microphone that corresponds to your vote. You will approximately 20 seconds to vote. Please press the button firmly.

After you've made your selection, the light

may continue to flash. If you are unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed.

So we will be voting on question 2A first, and this is whether the efficacy data provides substantial evidence of clinical benefit of reslizumab once every 4 weeks for the treatment of asthma in adults 18 years of age or older. So press the button that corresponds to your vote firmly.

(Vote taken.)

DR. WEBER: Will it stop flashing?

DR. OWNBY: No, it will not stop flashing or it may. Depends on how quickly you-all vote.

(Laughter.)

DR. HONG: For question 2A, we have 13 yeses, 1 no, and zero abstain.

DR. OWNBY: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did

into the record. And we'll start with Dr. Brittain on this side this time.

DR. BRITTAIN: This particular question, which I thought very easy, I think the efficacy of this dose had very strong results in all the efficacy endpoints, including the exacerbation, and just very easy.

DR. OWNBY: Dr. Dykewicz?

DR. DYKEWICZ: I did vote yes. I think in my own thought process, this is with the recognition that if you define a population of shall we say, a blood eosinophil count of 400 or greater, we did in the U.S. population see that there was a benefit in terms of FEV1. I am still concerned that we're not able to demonstrate or they were not able to demonstrate that the exacerbation rate was decreased, but I voted yes on the basis of FEV1.

DR. OWNBY: Dr. Greenberger?

DR. GREENBERGER: I voted yes. I believe there's substantial evidence of a clinically meaningful benefit, but I would like to see data in

the U.S. showing reduction in exacerbations.

DR. STOLLER: I voted yes. I'll refrain --

DR. OWNBY: I'm sorry. State your name.

DR. STOLLER: This is Stoller. I voted yes. I'll reiterate what I heard. I'm often fond in this setting of -- because it's a dichotomous vote yes/no, I'll give you my level of confidence in the yes as another axis because I often think we should plot level of confidence in the recommendation as a conditioning issue.

I would say that my level of confidence, particularly with regard to the issue at hand, licensing this for a United States population is low. On the one hand, I can't imagine, as was pointed out, reasons that the general experience couldn't extrapolate, but points have been made that would challenge the generalizability of a non-U.S. population to U.S. results. And by itself, the U.S. data are not, in my view, compelling. The totality of efficacy data are compelling, so that's what informed my vote.

DR. OWNBY: Dr. Yu?

DR. YU: I voted no, and I echo what my colleague just said here. We wish we have a skill or a level of your confidence.

I vote no, but also, I can see the absolute value does show that 3 milligram is effective. But taking into consideration of the inadequate coverage for U.S. population and also in comparison with the 0.3 dosage, there is lots of unanswered questions. So that's why I voted no.

DR. OWNBY: Dr. Connett?

DR. CONNETT: This is John Connett. I voted yes, although some subpopulations, it doesn't look like a strong effect. But it seems to me that there is pretty convincing evidence of an effect in reducing exacerbations and in improving lung function overall.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: Yes, Elaine Morrato, and I voted yes. And I agree with many of the points that Dr. Stoller just made. I too agree that the totality of the evidence was in support of approval, and I agree specifically with FDA's

conclusions that it was efficacious in reducing the asthma exacerbation frequency and improving lung function.

I would also like to add that I agree with the FDA that the lower dose appeared to be efficacious on trough FEV1 as well, although it wasn't studied for exacerbation.

DR. OWNBY: Dr. Weber?

DR. WEBER: Richard Weber. Yes, I voted yes also basically for the same reasons that have already been enumerated.

DR. OWNBY: Dr. Georas?

DR. GEORAS: Steve Georas. I voted yes. It seemed to me the clinical program met the primary efficacy endpoints.

DR. OWNBY: Dennis Ownby. I voted yes, although I'm concerned by the lack of efficacy in the U.S. data and specifically about African Americans.

Dr. Tracy?

DR. TRACY: Jim Tracy. I also voted yes. I thought there was substantial evidence to support

its approval.

DR. OWNBY: Ms. Holka?

MS. HOLKA: Andrea Holka. I voted yes. As a mother with two kids with asthma, I think it's very important to have different medications available, but the data for the U.S. is very concerning.

DR. OWNBY: Dr. Voynow?

DR. VOYNOW: Judy Voynow. I voted yes for all the reasons that have been stated, although I would also like to say I know we're not supposed to talk about labeling instructions. But I think since all the studies were done with a blood -- or the phase 3 studies were done with blood eosinophil counts above 400, that that should be important with respect to considerations of who receives the drug.

DR. OWNBY: Dr. Platts-Mills?

DR. PLATTS-MILLS: Tom Platts-Mills. I voted yes because the clinical effect was clear, and it's attractive that it is based on a criteria that can be used in normal practice, that is, an

eosinophil count. And I also voted yes -- and I was not bothered by the minor groups because with a disease as complicated as this, you don't expect to see -- I mean, you can't expect to see significant results within groups that small.

DR. OWNBY: If we could put the question back up. We'll now vote on question 2B, and that concerns children ages 12 to 17 years. Any other questions before voting on this?

(No response.)

DR. OWNBY: Same instructions, press the key that corresponds to your vote. Press it firmly. You can change your vote until they're all locked in.

(Vote taken.)

DR. HONG: Question 2B, we have zero yes, 14 nos, and zero abstain.

DR. OWNBY: We'll start on the other side.

Dr. Platts-Mills, if you'd like to tell us your vote, state your name and vote and reasons.

DR. PLATTS-MILLS: Tom Platts-Mills. I voted no because we're not offered data on the

pediatric age group. And that clearly, if it's thought that this product really is going to work in a pediatric age group, we would love to see a full study and preferably going younger than 12. So that having two groups younger than 12 and 12 to 17 or a proper pediatric group. That's why I voted no.

DR. OWNBY: Dr. Voynow?

DR. VOYNOW: Judy Voynow, I voted no. I agree with what Dr. Platts-Mills says, and as well really, I felt they didn't meet the primary outcome. So, no.

DR. OWNBY: Ms. Holka?

MS. HOLKA: Andrea Holka. I voted no. There's just not enough data.

DR. OWNBY: Dr. Tracy?

DR. TRACY: Jim Tracy. I also voted no. It failed to meet primary outcome, and simply not enough people.

DR. OWNBY: Dennis Ownby. I voted no for the reasons already stated.

Dr. Georas?

DR. GEORAS: Steve Georas. I voted no. Nothing to add to the already stated reasons. Thank you.

DR. OWNBY: Dr. Weber?

DR. WEBER: Richard Weber. I voted no also, and looking at the graphs in one of the studies, the effect was favored placebo distinctly and didn't cross the 1 point. And in the other, it was right on the neutral point. So all together, very non-compelling data.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: Elaine Morrato. I voted no for reasons stated, and it just did not meet the definition of substantial evidence.

DR. OWNBY: Dr. Connett?

DR. CONNETT: This is John Connett, and I voted no. The numbers are just too small.

DR. OWNBY: Dr. Yu?

DR. YU: Yes, I vote no for the reason my colleagues have said. But I do want to comment that I would like to see the sponsor collect more data to study this particular population. In

general, 18 years or older, for consumers, we like to have different treatment options that can reduce the cost for the treatment, and also, we want to just have options so that for both safety and the efficacy.

DR. OWNBY: Dr. Stoller?

DR. STOLLER: This is Stoller. I voted no for the reasons stated. I would say that if there's a specific desire for labeling indication in this group, and I think there's a clinical appetite for that, as was stated, there ought to be an explicit study that recruits patients in these age ranges to look at it, not as a subset of a larger study.

DR. OWNBY: Dr. Greenberger?

DR. GREENBERGER: Paul Greenberger. I voted no. The data aren't there. And because of the importance and this unmet need in children and adolescents, I hope that the sponsor and agency can work together to get this area explored.

DR. OWNBY: Dr. Dykewicz?

DR. DYKEWICZ: Mark Dykewicz, voted no for

reasons already stated. Again, would encourage the sponsor to undertake studies in this population to establish effectiveness.

DR. OWNBY: Dr. Brittain?

DR. BRITTAIN: Again, for me, this was an easy in that there was clearly no substantial evidence. All the evidence we had was -- we had limited data, and all the evidence was going in the wrong direction, and agreed that a study should be done in children.

DR. OWNBY: Thank you.

We'll move on to question 3. Discuss the safety data for reslizumab 3 milligrams per kilo IV administered once every 4 weeks with specific considerations for the findings of anaphylaxis and muscle toxicity. Comment on the potential impact of additional dose-ranging data or product attributes, that is, alpha-gal, when discussing the anaphylaxis safety signal.

Dr. Platts-Mills?

DR. PLATTS-MILLS: I'd like to address the anaphylaxis question. First of all, I think the

company has adequately provided evidence that these rare anaphylaxis events were not due to alpha-gal. If it's true that the molecule is not glycosylated on the FAB, then it's very unlikely that that what's happening.

It would be nice to see -- I'm assuming the measurements of IgE to alpha-gal in the sera were less than 0.1 or less than 0.35. I'd like an answer on that. Which number did you have?

DR. SHAH: Less than 0.3.

DR. OWNBY: Could we put the microphone on for Dr. Shah, please.

DR. SHAH: Do you want -- let me have Dr. Laurie Pukac, who actually knows all the data, to speak to that.

DR. PUKAC: Yes. The measurement -- sorry. Dr. Laurie Pukac, bioanalytics. The measurements were actually less than 0.3. And one of the reasons for that was because we had to dilute the samples to provide adequate volume. So that was the bottom of the range of the assay.

DR. PLATTS-MILLS: Oh, I see. You diluted

the 1 and 3, and the actual value given was less than 0.1, and that you modified.

DR. PUKAC: That's correct.

DR. PLATTS-MILLS: Fine. Have you made any attempt to measure IgE to the molecule itself?

DR. PUKAC: We're working with the FDA. We're actually the -- we have a assay in development for that.

DR. PLATTS-MILLS: As far as the other -- so let's put cetuximab, the alpha-gal on one side. It's very unlikely to be explanation of any of these reactions.

The unknown mechanisms for anaphylaxis, you can't exclude a dose response. Remember that there is the old contrast media model where you actually need quite a large dose before you get anaphylactic events. So that you can't be absolutely sure that there isn't a difference between 3 milligrams and 0.3 milligrams in an anaphylaxis event given that we don't know what it is.

But I see that situation as no different from the situation with many other monoclonal

antibodies, where we have a persistent anaphylaxis rate that is including Xolair where we do not understand it, and it's obviously important to keep looking.

DR. OWNBY: Dr. Weber?

DR. WEBER: The other thing to consider with an IV administration is that it may not be the drug itself but rather perhaps the detergent like the Tween 80, which is frequently added, and that this can give you an anaphylactoid complement-mediated anaphylactic-like reaction. And I don't think that should be entirely disregarded.

DR. OWNBY: I thought with the formulary listed, the formulation, there weren't other excipients. But could someone from the sponsor comment? Are there other excipients with this molecule that might explain an adverse reaction?

DR. BOCK: Jason Bock, CMC development. So there are other excipients to stabilize the product, but polysorbate or Tween is not one of them. The other excipients are salts and sugars.

DR. OWNBY: And none of them have ever been

associated with systemic reactions, to your knowledge?

DR. BOCK: I can't comment on that. It's sucrose acetate.

DR. KARIMI-SHAH: This is Banu Karimi-Shah from the FDA. For the sponsor, just other than the addition of the active drug, is there a difference between placebo and the drug product in terms of excipients? Because that would go towards the question of whether or not --

DR. BOCK: No. The placebo is the same components as the active without the active ingredient.

DR. WEBER: However, there was one reaction in placebo, if I remember correctly.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: I just might provide a comment just for the record as we think about in terms of the overall sample and years of exposure, so commenting on kind of the size of the safety database.

Looking at the information, it seems to be

robust in meeting the standards of what's necessary for a chronic drug for regulatory approval. It is a larger global clinical program, as the sponsor notes, with about 1593 patient-years of exposure, and 950 patients with 12 months or more of exposure.

So therefore, I agree with the FDA's assessment that the safety signals that they are concerned about are real, the anaphylaxis and the myopathy. And the reason that seeing them in a clinical program is something that we should take note as we think about the overall benefit-risk.

I'll just iterate also from the adolescent standpoint, though, the sample size is small, and so really is inadequate to be able to assess safety in those patients even if it does look similar to what the placebo kids looked like.

DR. OWNBY: Dr. Dykewicz, and then Dr. Connett.

DR. DYKEWICZ: Mark Dykewicz. One thing I wanted to just pose to members of the committee, some who may be far more learned in terms of IgG

subclass structure and potential effects, that that would have on risk for anaphylaxis. Of course, in the landscape of recent regulatory review of anti-IL-5 agents, I'm struck by the fact that mepolizumab was not presenting this level of concern about anaphylaxis.

Maybe also to the FDA, my recollection is that's an IgG1 versus an IgG4 antibody in this case with reslizumab. The agency had proposed a mechanism that IgG4s have unstable disulfide bond and that could break down into half antibodies, and therefore, in vivo, open the possibility of forming full antibodies that are bispecific.

So I'm struggling with the thought, is the fact that this is an IgG4 versus an IgG1, one possible explanation why we're seeing more of a signal with this anti-IL-5 rather than the other previously approved anti-IL-5.

Any comments from the rest of the group?

DR. PEDRAS-VASCONCELOS: This is Joao Pedras-Vasconcelos, FDA, immunogenicity. We struggled with exactly the same issue, and we went

through a series of speculations and exercises and mental exercises to try to conceive of the notion of how that could happen. We couldn't do it.

The idea typically when you have these bispecifics, they tend to be in unusual situations. They tend to be in conditions, chronic conditions, or for instance, my understanding is in patients that have desensitization to two different antigens that sometimes you end up with IgG4s, which are actually often associated with the successful desensitization protocols. IgG4s which could in theory actually have different specificity simply if you have -- if you desensitize a patient to two different antigens and if you have a successful desensitization therapy, you end up with some circumstances of IgG4s where actually are monovalent because they only bind one specific antigen but they are together.

So they are bispecific in that sense, and they tend to be thought to play a role in down-regulating effective responses. And they're actually interfering with IgE-mediated signals and

infector cells. So we struggled with that same issue.

Relative to mepo, yes, you are correct. It is an IgG1, and this is an IgG4. As was pointed out by Dr. Platts-Mills in his questions, there was no modification in this IgG4, which has been associated, seen, with other potential products where they wouldn't have this association.

So this is still an old classic IgG4, so to speak. But at this moment, we couldn't really come to grips with the possibility of this IgG4 contributing to increase in anaphylaxis.

DR. OWNBY: I'm going to let Dr. Shah make a comment and then Dr. Platts-Mills.

DR. SHAH: I think one of the things we do to try to understand this risk, which is the issue of immunogenicity, because that's what we are trying to decipher here is, is this molecule more immunogenic because of these structural changes. And I think the ADA data that we have shows that it is quite reassuring. If you compare it to mepo, which some of you were there, their level was not

much different than where ours is.

So immunogenicity is really the canary in the coal mine. It tells us is this molecule at risk for generating immune response in humans and what is that level of immune response. And what we see with this molecule is quite low and very transient immunogenicity concerns.

DR. DYKEWICZ: If I might add, that does not preclude, in my mind, the ability of the product to generate anaphylaxis on a different mechanistic basis.

DR. OWNBY: Dr. Platts-Mills, you had a comment?

DR. PLATTS-MILLS: I'd just like to comment that there's a possibility that the bivalent could cause trouble. Remember, there are some molecules that are in the circulation that could have one arm directed at IL-5 and the other arm directed at some allergen.

But the molecules that are being infused -- and it's the anaphylaxis or the type of infusion we're worried about, those are all

anti-IL-5. So that they're not bivalent when they're infused, and they can't be because there's only one molecule in the preparation. So even if they split and recombine, they're not going to be bispecific.

So I agree with the FDA. I cannot conceive of a mechanism where that is causing trouble in this situation.

Could I also just say something about the myopathy signal? I think the thing that's -- I mean, I know that CPK can go up with lots of things. Intramuscular injections can give you bad rises, which are very confusing. I've seen that happen clinically.

So these patients, some of the patients are receiving allergy shots. Do allergy shots give a rise in CPK? I don't know of much data about that. And in all the data I've seen on this molecule, if you leave the patients alone and continue injections, it doesn't go on up, and you don't see a persistence to the problem. So it's overall very reassuring.

DR. OWNBY: One of the things I'm concerned about with this is that I believe in all these studies -- and the sponsor can correct me if I'm wrong -- women of reproductive potential were excluded. And yet if this is approved, almost certainly women of reproductive potential will be receiving it.

If there's any signal with muscle and this is going to be transported across the placenta, is that going to present a higher risk?

DR. PLATTS-MILLS: There were two or three pregnancies.

DR. ZANGRILLI: Women of reproductive potential were not excluded.

DR. OWNBY: So how many pregnancies occurred, and was there any follow-up of those offspring?

DR. SHALIT: There were eight pregnancies on reslizumab, two ended with elective abortions. There was one missing case, and the five cases were healthy newborn. One of them had physiological jaundice. And we have information follow-up of

8 weeks old for them, and no adversities.

DR. OWNBY: Thank you. Any other -- Dr. Connett?

DR. CONNETT: I wonder if the sponsor could put up slide CE-19 again? We've seen it several times. So this slide indicates that the eosinophil counts went from something over 500 -- I don't know how much over -- down to less than a tenth of that, 90 percent reduction in the eosinophil counts.

I would remind us that FDA has said in addition to the data that we have on anaphylaxis and other effects. They mentioned the malignancy issue. The paper that I cited indicates that for the highest tertile in the population of eosinophil counts, the relative risk of colon cancer was 0.58 with a confidence interval that was well separated from 1.

It just seems to me here that you're inducing a drastic reduction in the eosinophil counts. And if somebody is going to be taking this for a long time, which I would expect, there's going to be substantial risk, if the epidemiologic

data is true, of at least colon cancer, possibly other cancers.

It would seem to me that the remedy here would be some kind of systematic review of the literature on epidemiology associated with eosinophil counts and cancer in general, possible meta-analysis, both by the company and by the FDA. I think both of those are well justified in this case.

DR. OWNBY: Dr. Platts-Mills.

DR. PLATTS-MILLS: Can we leave that slide up? Because I asked a question about this earlier, about whether the basophil counts go down, and I think someone was about to answer it. I think you stood up, didn't you?

Someone was going to --

DR. ZANGRILLI: Doctor, I'd have to check on that. The complete blood cell differential did get basophil counts, but they weren't -- we didn't look carefully at them, so I'm not sure. Please.

DR. PLATTS-MILLS: And I think I'm right that there's an IL-5 receptor in relation to

basophils.

DR. ZANGRILLI: Right. So reslizumab definitely, which is an anti-IL-5 receptor antibody, will knock out basophils. There's no particular reason we should. I'm not sure about that, but you're right. The basophils do have an IL-5 receptor.

DR. PLATTS-MILLS: The other issue that Dennis started to bring up is the issue of whether these monoclonal antibodies can carry things across the placenta, which is highly relevant to Xolair because Xolair may well be able to -- the passage across the placenta, IgE is destroyed, but IgG molecules are protected by a receptor called Fc gamma Rn. And Fc gamma Rn protected IgG, but it also protects molecules bound to the IgG. And it's not clear whether it will protect IgE, but it's perfectly possible that anti-IgE during pregnancy could carry IgE across into the baby.

With this molecule, carrying IL-5 across, it's very difficult to see how it -- and I don't know whether the company has any views on whether

that could possibly have an effect on the baby or the anti-IL-5 could have an effect on the baby. You haven't got any data.

DR. SHAH: No, not in humans, of course. We do have preclinical data. We look at repro tox, and I don't know if our preclinical expert could comment on some of the preclinical data. But I think the short answer is there is no evidence of any concerns in those repro tox and fertility-type studies.

DR. OWNBY: Thank you. I have Dr. Greenberger and then Dr. Morrato.

DR. GREENBERGER: This has to do with people receiving this medicine long-term. I would say that's not going to be the case because I would think practice parameters would come out, and professional societies could review information and see that, say, if a person is on this treatment for four months and has no meaningful benefit, perhaps there's not going to be a benefit. So a patient would not prudently be continued on this product, for example.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: I just wanted to add, just so it's I guess on the record, that a sample size that's adequate to assess approval does not necessarily mean that we don't do very rigorous postmarketing pharmacovigilance. And I would expect that for the key cases in which we have limited information in the data set on these safety issues that are being discussed, that they be prospectively evaluated and not just rely on total spontaneous report. But I know for certain events, companies can come up with protocols, that when a case like that comes in there, it's more rigorous case evaluation.

So that would relate to the anaphylactic and the myopathy. And I would agree also in terms of the long-term mutagenicity, those are going to require long-term kinds of studies -- and probably not just this company but looking at eosinophil treatment more broadly, if other drugs are also approved -- to be part of the postmarketing planning.

DR. OWNBY: Dr. Tracy?

DR. TRACY: Just going a little bit back with what Dr. Platts-Mills said about the muscle toxicity issues, not that it would be reason to not approve it -- and it kind of goes back to what Dr. Morrato just mentioned, too, about these musculoskeletal symptoms were higher in the treatment group, and we really don't know the mechanism. So I think vigilance downstream is going to be really important in this population.

DR. OWNBY: Vasconcelos?

DR. PEDRAS-VASCONCELOS: Yes. Joao Pedras-Vasconcelos, immunogenicity, FDA. I wanted to address the question brought up by Dr. Platts-Mills and the issue of IgG4 potentially crossing the placenta.

There's been studies from the '80s that show IgG4 does cross placenta. They did measurements in both early stage and late stage pregnancies, and they also looked at the levels in the embryo and in babies just after they were born. And they were able to show that IgG4 was able to cross the

placenta.

However, addressing this issue -- and Dr. Platts-Mills is correct, the Fc mechanism -- the Fc Rn, which is what grabs the immunoglobulin and plays a role in getting across the placenta. However, there's an endocytic step, and that endocytic step, there's disassociation, potential disassociation of the IL-5 because of the change in the pH. And so while it could still maintain itself in there, it may be the IL-5 wouldn't necessarily be crossed over the placenta.

DR. PLATTS-MILLS: You've declared war.

(Laughter.)

DR. PLATTS-MILLS: If you want to elude antibodies off a column of antigen, pH 6 won't do it. And the pH cathepsin activates is 6, and the Fc gamma Rn raises its affinity for G at about 6. To get things off a column, you need to go below 3.5. So I take your point entirely, but we can continue to fight.

DR. OWNBY: Any further discussion of this question before we move on to the next voting

question?

(No response.)

DR. OWNBY: If we could have question 4, please. We've had a long discussion. Now, is the safety profile of reslizumab 3 milligrams per kilo IV administered once every 4 weeks adequate to support approval for patients with asthma? If not, what further data should be obtained?

Any discussion, comments? Dr. Morrato?

DR. MORRATO: By patients, do we mean 12 to -- all right. Do you want us to differentiate in our vote, if we make a differentiation like we did in the efficacy, or do you want -- how would you like us to -- think of it more broadly and then qualify it for an age group or for a subgroup?

DR. KARIMI-SHAH: The latter, so think of it more broadly and then just qualify your comment. Thank you.

DR. OWNBY: So we're thinking of the entire age group 12 and older for this question. Any other clarifications?

(No response.)

DR. OWNBY: So it's time to cast your vote. Is the safety profile of reslizumab 3 milligrams per kilo IV administered once every 4 weeks adequate to support approval for patients with asthma?

(Vote taken.)

DR. HONG: Question 4, we have 11 yeses, 3 nos, and zero abstain.

DR. OWNBY: We'll start back on this side again. Dr. Brittain.

DR. BRITTAIN: Unlike the efficacy question, I found this one much harder to answer. I mean, obviously, there are safety concerns. I think even though the question was split out from the efficacy, in the end, it's always going to be a risk-benefit consideration. And as a non-clinician, it's hard for me to make that assessment.

But it seemed like the safety concerns that have been revealed may be tolerable given the benefit of the drug. And of course, this is one -- I mean, this is where again we were all

really hurt in not having the data on another dose because that's the sort of unanswerable question in the background is, as we have talked about all day, is there a dose with similar efficacy that would have less toxicity?

DR. OWNBY: Dr. Dykewicz.

DR. DYKEWICZ: I think the safety signal about anaphylaxis is real, but the question is posed in a different format about -- finally get down to approval. But I do think that one could make a case that there's a relatively low amount of anaphylaxis, but it's real. I think in the end, in the clinician's mind, there's going to be a question about alternative agents and whether this agent has a higher safety concern from an anaphylaxis standpoint, and that will enter into the decision as to which product to potentially use.

I would say that from the standpoint of the CK elevations, I am reassured by the fact that the patients continued to receive, for the most part, the agent reslizumab, and there was not some

persistence of the CK.

I certainly would think it important to take a look at why there is the higher incidence of the myalgia and muscular complaints after administration. That type of an assessment might be looking at acute elevations or not in CK or aldolase. I do think that's an area of scrutiny, but in the entire context of consideration of safety, I don't believe there are enough safety concerns that it would absolutely preclude the approval of the drug.

DR. OWNBY: Dr. Greenberger.

DR. GREENBERGER: I voted yes, and I do believe the issue regarding anaphylaxis has been covered, that there isn't evidence for missing any cases of anaphylaxis. I already stated earlier about exploring the effect of intense exercise on the day of the infusions so we can get information regarding that.

DR. STOLLER: This is Stoller. I voted no. My interpretation of this was really on technical grounds in a sense that really related to criterion

4B, do we have sufficient information. And I was considering the totality of data 12 to 17 and adults. I think there really isn't enough data on the -- to Dr. Morrato's question, enough about children to endorse a totality of safety issue.

My decision was not informed by concern about anaphylaxis. I'm actually not concerned about that. I think that's been well explicated. To the extent to which there is uncertainty, leaving aside the malignancy and long-term issues -- although I take Dr. Greenberger's point. I think as a clinician, we'd be unlikely to submit patients to once weekly drug for long periods of time without short-term benefit, leaving aside issues of costs, which are undoubtedly will be significant in the clinical utilization of such agents.

But it was really related to the fact of a bit of a vacuum of information about CPK. The question has been raised. I don't think the kinetic data about CPKs, checking serially over once a month, provides enough information to

discount the possibility. And there were some significant elevations, 10, 20,000 of CPK, admittedly without renal failure. That's reassuring, but as a signal that's unexplained, that's what informed my concern in voting no.

DR. OWNBY: Dr. Yu?

DR. YU: Yes, Yanling Yu. I voted no because the question is, is there any adequate -- evidence to adequately support approval. So I evaluated all the evidence presented to us. I do not think there is adequate evidence, particularly like adolescent population, safety signal.

Also, I'm still a little concerned about anaphylaxis signal not because that the assurance we heard from the panelists and from the sponsor. I'm concerned about just the data as a time. The sponsor acknowledged that they should have done it. They should have collected those data, and I feel it's a little sloppy for doing that.

I still believe that when the drug is proved and out on the market, there will be lots of people

exposed, and we will have a different population, different disease process and background, and we've got to be really careful on that. So being on the cautious side, I said not enough adequate data. That's why I voted no.

DR. OWNBY: Dr. Connett?

DR. CONNETT: This is John Connett. I voted no. I do have concerns about safety with regard to general populations with regard to malignancies. I think suggested remedies might be to carry out a systematic review or a meta-analysis of data and to have fairly strong labeling that includes some warnings about what the side effects might be. And postmarketing surveillance, I don't have huge faith in that, but it would seem like that's justified in this case.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: Elaine Morrato, and I voted yes. I felt there was, as many have stated, overall a sufficiently sized safety database in order to assess the profile. I had a couple of caveats that have been mentioned as well. I think

it requires an active postmarketing pharmacovigilance plan for the safety signals that are of concern.

I agree it's not adequately sized for adolescents, and I'll cover that in my vote on approvability. And I also agree it doesn't necessarily address the question that a lower dose could be as effective and possibly safer.

I do want to add that I believe and want to think that clinicians and patients will stop medication if it's not working. I think in practice, that can be problematic for many. If you're using, for example, asthma exacerbation as your benchmark and that occurs over a year or two to try and understand what your pre-rate is versus your post and whether or not it's having any effect or not, it's not like this medication necessarily takes people that are having multiple exacerbations down to none.

So it will difficult, I think, in practice to determine how well it's working for patients. And oftentimes, the inertia is to stay on medicine.

So I think we will end up with many patients taking it long term, and therefore, the long-term safety follow-up is important.

DR. OWNBY: Dr. Weber?

DR. WEBER: Richard Weber. I voted yes. I think some of the concerns about adverse effects, certainly the anaphylaxis, since this has to be given intravenously, it would at least be given in the circumstance where there should be someone there to handle that appropriately, not like something that could be self-administered at home and could be a risk.

I think the issues of the age of administration has already been addressed in one of the previous discussions, so I think that becomes a moot issue.

DR. OWNBY: Dr. Georas?

DR. GEORAS: Yes. Steve Georas. I voted yes. In terms of the anaphylaxis issue, I'd like to commend the agency for investigating this alpha-gal story. I thought that was well done, and I was reassured by the data presented and by

Dr. Platts-Mills' opinion there. And it seems like we're dealing with a idiopathic, maybe class effective monoclonal antibodies where we'll have to decide the risk-benefit analysis at the bedside.

The CK elevation I think was adequately discussed, and I was reassured by the fact that these seemed to be very idiosyncratic and did not persist with repeated dosing.

I'd like to once again bring up my concerns about malignancy, which I think we've discussed and strongly encourage the agency to put in place some kind of surveillance monitoring as these IL-5 pathway antagonists are going to be moving into the clinic over the next few years since I think the signal there, if present, will be small.

I was reassured to hear that the malignancy signal was comparable to what you had seen in other biologics, but I think the rationale for our concerns is probably stronger with eosinophil-targeted pathway than, say, anti-IgE. So I'll stop there. Thanks.

DR. OWNBY: Dennis Ownby, I somewhat

reluctantly voted yes. I'm very conflicted. I don't think we have adequate information for the 12- to 17-year age group, although I'm somewhat reassured that the signal wasn't picked up in their eosinophilic esophagitis studies. And I'm hoping that that will hold, that it's not a problem unique to younger people.

But I think that this is a drug that clinicians will probably use very cautiously and maybe with a proviso that they'll watch CPKs and that they'll be very vigilant about anaphylaxis. So I'm placing faith on our practicing physicians that this will not be a major problem.

Dr. Tracy?

DR. TRACY: Jim Tracy, since I first got the briefing materials some time ago, I've always been confident in the anaphylaxis issue. I think it seems similar to other monoclonals that we've looked at in the past.

My biggest concern coming to this meeting was really the musculoskeletal CPK stuff, and I think that that's been adequately addressed. I

wish we knew the mechanism, but maybe someday.

DR. OWNBY: Ms. Holka?

MS. HOLKA: Andrea Holka. I did vote yes. Very fond of Dr. Morrato's idea for postmarketing vigilance and surveillance. I know anaphylaxis is an issue any time you put something in your body medication-wise, but I don't know what the magic number is as far as too many. I don't know. But I do think that that's something that needs to be taken a look at and watched over time.

DR. OWNBY: Dr. Voynow?

DR. VOYNOW: So I voted yes that there was adequate safety, but I just want to make the following comments. To me, it has to be within the context that this should really only be prescribed for severe asthmatics who have a blood eosinophil count more than 400. So in that setting, I think that the safety data we've seen would be tolerable with the following caveats.

I agree with Dr. Connett, there needs to be a strong warning so that physicians are very vigilant, again, about anaphylaxis and monitoring

patients for that, for CPK monitoring, for myositis. And I would also agree that there should be postmarketing surveillance for malignancy, because for those patients that this is effective for, they are going to be on it for decades.

Then my last comment is if this question had been split up by age, I bet almost all of us would agree that there's insufficient safety data in the setting of insufficient efficacy data -- so let me speak for myself -- for the 12- to 17-year olds. So in that setting, I would probably have said no.

DR. OWNBY: Dr. Platts-Mills?

DR. PLATTS-MILLS: Tom Platts-Mills. I voted yes. I would like to just talk about the issue of infusions. There's very strong pressure going on nationally now to get IV/IG, that is intravenous immunointraglobulin infusions, at home. The insurance companies are progressively denying payment for IV infusions in the hospital, and so it really needs to be decided whether that's a possibility for this product. And I think that that's an issue that needs to be resolved. But

within a physician's office, I think the information we have provides reassurance.

DR. OWNBY: Thank you very much. We can move on to the last question.

Surprise, surprise, this is the last question. Do available efficacy and safety data support approval of reslizumab 3 milligrams per kilo IV every 4 weeks for the treatment of patients with asthma in adults 18 years of age and older? If not, what further data should be obtained, and B, in children 12 to 17 years of age?

My understanding is again, we will be voting as two separate questions. We'll vote first on question A and then on question B by the age groups. So are there any clarifications or discussions of this question before we vote?

(No response.)

DR. OWNBY: Seeing none, then we will vote on question 5, do the available efficacy and safety data support approval in adults 18 years of age and older? Remember, press firmly. I always think we ought to have a little Jeopardy music here or

whatever at this stage.

(Laughter.)

(Vote taken.)

DR. HONG: Question 5A, we have 11 yeses, 3 nos, and zero abstain.

DR. OWNBY: Okay. Dr. Platts-Mills, I believe we are back to you.

DR. PLATTS-MILLS: I voted yes, and I think I've made my views quite clear.

DR. OWNBY: Dr. Voynow?

DR. VOYNOW: I voted yes, and I've also discussed all of my reasons for that.

DR. OWNBY: Ms. Holka?

MS. HOLKA: Andrea Holka. I voted yes for reasons already stated.

DR. OWNBY: Dr. Tracy?

DR. TRACY: Jim Tracy. I also voted yes for the reasons previously stated.

DR. OWNBY: Dennis Ownby. I voted yes.

Dr. Georas?

DR. GEORAS: Yes, I voted yes. We need to all balance risk-benefit, and what carried the day

for me is the unmet need in my patients.

DR. OWNBY: Dr. Weber?

DR. WEBER: Richard Weber. I voted yes, also ditto to the previous comments.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: Elaine Morrato. I voted yes, consistent with my previous statements. I'd just like to also add I'm a little worried in how the definition of the eosinophil phenotype will actually play out in practice and be operationalized into clinical practice, recognizing that if this product's approved, there are different thresholds that were used in this trial and definitions than in the other drug.

So how will this all get played out as clinicians are working through this? And then the blood levels may not even be predictive. So I think it's important that we not just look at safety pharmacovigilance postmarketing but perhaps also surveillance of what types of patients end up on the product. Is it the type of patient that was in the trials, or does it get much more broadly

interpreted when it gets into clinical practice?

Because the benefit-risk assessment, as Dr. Voynow was saying, is in the context of who was in these studies. And if practice gets broader than that faster than we have data, that's when we have problems. So I think there should be surveillance also in what kinds of patients are being put on the product and how clinicians are thinking about the phenotype in practice.

DR. OWNBY: Dr. Connett?

DR. CONNETT: This is John Connett. I voted no. Like Dr. Morrato, I'm being consistent with my previous vote on safety, which I don't think has been demonstrated. And I think that, as I've said before, if it goes ahead, then there needs to be postmarketing surveillance carried out. But I don't see enough evidence right now that it's a completely safe product.

DR. OWNBY: Dr. Yu?

DR. YU: Thank you. Yanling Yu. I voted no consistent with my previous vote. I just want to reiterate -- I'm sorry. I just want to say again

that as consumers and patients, we do want to have more treatment options to cut down the cost, but we do want to have a higher benefit and risk ratio. But for this particular product, it seems like we have more unanswered questions than we can answer, in particular the doses and there are some other issues. We don't even know whether this safety issue and whether the efficacy versus the risk is the same as a lower dose. At least, I don't know.

So that's why I really highly encourage the sponsors, if approved -- whether or not approval, approved or not, to collect more data to look at lower doses and to evaluate efficacy and safety signals.

DR. OWNBY: Dr. Stoller?

DR. STOLLER: This is Stoller. I voted no in the context of my prior comments on safety. I'll make one comment that since this question is stratified by age, again, in keeping in my prior comments about the level of confidence in the no vote, my level of confidence in no here is relatively small because I think there's a strong

unmet clinical need. But the no is predicated on really having insufficient information to address the CK kinetics, and the fact that that did translate into some instances, albeit rare, of significant CK elevations, admittedly in a few cases not sustainable when checked a month later despite continued later. So I had a low level of confidence in no, but I voted no.

DR. OWNBY: Dr. Greenberger?

DR. GREENBERGER: I voted yes. The unmet need, as I said, for steps 4, 5, and 6 asthma is very, very high. I would like to say that the vote yes implies that the blood eosinophil count is 400 or more. And I also want to put out that in the study all patients responded to albuterol, 12 percent or more. So that's a phenotype that may be expected in most of the severe patients but not all, and I just wanted to point that out.

DR. OWNBY: Dr. Dykewicz?

DR. DYKEWICZ: Mark Dykewicz, votes yes. Of course, echoing comments of the others. There is this issue then, though, as to even though we're

not supposed to discuss labeling, what patient severity would be appropriate for treatment. And I am mindful that up to, in one study, 87 percent of the patients were also using a long-acting beta agonist on top of inhaled corticosteroids. Other patients were using leukotriene receptor antagonists. So in a risk-benefit assessment, I would view this as a drug that would be more towards, if you will, step 5 or 6.

DR. OWNBY: Dr. Brittain?

DR. BRITTAIN: Yes, I voted yes with the same caveat that I had for the safety vote that I do wonder whether there's a dose that has a better risk-benefit profile. And it's probably not practical to do another study post-approval on this, but I would think they would be equipoise to consider a smaller dose. So maybe it could be done.

DR. OWNBY: Thank you all. That's one more vote. If we could have the question back, same question, but now we're voting on part B in children 12 to 17 years of age. Do the available

efficacy and safety data support approval? Press yes/no. Press it firmly.

(Vote taken.)

DR. HONG: For question 5B, we have zero yeses, 14 nos, and zero abstain.

DR. OWNBY: Dr. Brittain, we're back to you.

DR. BRITTAIN: Okay. So again, this is based on previous votes, and I leave it to my clinical colleagues to provide recommendations about what sort of study needs to happen now in children.

DR. OWNBY: Dr. Dykewicz?

DR. DYKEWICZ: No additional comments other than those already made.

DR. OWNBY: Dr. Greenberger?

DR. GREENBERGER: No additional comments.

DR. OWNBY: Dr. Stoller?

DR. STOLLER: I voted no on the strength of my prior comments about lack of efficacy. I would say just in the general context of the remarks made, like Dr. Connett, I have relatively less faith in the postmarketing assessment and the

impact on management of such studies. So when there is a safety concern, my bias is prospective rather than retrospective in general.

DR. OWNBY: Dr. Yu?

DR. YU: Yes, I voted no based on all the reasons that I stated.

DR. OWNBY: Dr. Connett?

DR. CONNETT: I voted no in this age range, but I would note also that the numbers in the upper age range, over 65, are actually quite small, also.

DR. OWNBY: Dr. Morrato?

DR. MORRATO: Elaine Morrato, and I voted no for the reasons I've stated.

DR. OWNBY: Dr. Weber?

DR. WEBER: Richard Weber, I voted no also, again, in agreement with my colleagues.

DR. OWNBY: Dr. Georas?

DR. GEORAS: Yes. Steve Georas. I voted no. There's no compelling efficacy signal, and I was concerned about the safety as well.

DR. OWNBY: Dennis Ownby. I voted no. In this age group and younger, I'm very concerned that

we don't have a broader range of dosing to choose from and to justify the current recommended dose.

Dr. Tracy?

DR. TRACY: Jim Tracy. I voted no consistent with my two previous votes.

DR. OWNBY: Ms. Holka?

MS. HOLKA: Andrea Holka. I voted no for reasons already stated.

DR. OWNBY: Dr. Voynow?

DR. VOYNOW: I voted no for the reasons I've previously stated.

DR. OWNBY: Dr. Platts-Mills?

DR. PLATTS-MILLS: I voted no despite the apparent agreement with my colleagues.

(Laughter.)

DR. OWNBY: Okay. Before we adjourn, are there any last comments from the FDA?

DR. KARIMI-SHAH: Hi, this is Banu Karimi-Shah from the FDA. On behalf of all of my colleagues here and in the back, we'd like to thank this advisory committee and Dr. Ownby very much for your preparation for this meeting and all your

discussion today. It's very, very helpful to us. Thank you very much.

Adjournment

DR. OWNBY: I'm sorry I forced you right through your afternoon break, but recognizing we're finishing early because of it. Panel members, please take all your personal belongings with you as the room is cleaned at the end of the day. All materials left on the table would be disposed of. Please remember to drop off your badge at the registration table so they can be recycled.

Now we will adjourn the meeting. Thank you.

(Whereupon, at 3:44 p.m., the meeting was adjourned.)