FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Pulmonary-Allergy Drugs Advisory Committee
Ecallantide for the Treatment of
Acute Attacks of Hereditary Angioedema
Wednesday, February 4, 2009
8:30 a.m.

Hilton Washington D.C./Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

MEETING ROSTER

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE VOTING MEMBERS:

PAULA G. CARVALHO, M.D.
Director, Intensive Care Unit
VA Medical Center/Boise
500 West Fort Street
Boise, Idaho 83702

MICHAEL B. FOGGS, M.D.
Chief of Allergy, Asthma & Immunology
Department of Medicine
Advocate Health Center
2545 S. Martin Luther King Drive
Chicago, Illinois 60616

RICHARD W. HONSINGER, M.D.
Los Alamos Medical Center Clinic, Ltd.
3917 West Road
Los Alamos, New Mexico 87544

(Roster continued on the next page.)

ROSTER (continued):

NON-VOTING MEMBERS:

RICHARD C. HUBBARD, M.D. (Industry Representative)
Senior Director, External Medical Affairs
International Office of the Chief Medical Officer
Pfizer, Inc.
235 East 42nd Street
New York, New York 10017

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE VOTING MEMBERS:

MICHAEL PROSCHAN, Ph.D.
Biostatistics Research Branch
National Institute of Allergy and Infectious Diseases
National Institutes of Health
6700A Rockledge Drive, Room 5140
Bethesda, Maryland 20892

(Roster continued on the next page.)

ROSTER (continued):

BLOOD PRODUCTS ADVISORY COMMITTEE (CENTER FOR BIOLOGICS EVALUATION AND RESEARCH) VOTING MEMBERS:

MARK BALLOW, M.D.
Interim Chair, Department of Pediatrics
Chief, Division of Allergy & Immunology
Women and Children's Hospital of Buffalo
219 Bryant Street
Buffalo, New York 14222

TEMPORARY VOTING MEMBERS:

LAWRENCE BORISH, M.D.
Professor of Medicine
Asthma and Allergic Disease Center
University of Virginia Health System
Charlottesville, Virginia 22908

(Roster continued on the next page.)

ROSTER (continued):

TEMPORARY VOTING MEMBERS (continued):

REBECCA GRUCHALLA, M.D., Ph.D.
Associate Professor of Internal Medicine
Department of Internal Medicine
University of Texas Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, Texas 75390

WILLIAM CALHOUN, M.D.
Sealy and Smith Distinguished Professor
Vice Chair for Research
Department of Internal Medicine
University of Texas Medical Branch
4118 John Sealy Annex, Route 0568
301 University Boulevard
Galveston, Texas 77555

(Roster continued on the next page.)

ROSTER (continued):

TEMPORARY VOTING MEMBERS (continued):

PETER TERRY, M.D.
Professor of Medicine
Johns Hopkins Medical Institutions
Division of Pulmonary and Critical Care Medicine
1830 E. Monument Street, Suite 500
Baltimore, Maryland 21205

JOHN HOIDAL, M.D.
Professor of Medicine
Chair, Department of Internal Medicine
The Clarence M. and Ruth N. Birrer
Presidential Endowed Chair
30 North 1900 East
4C104 SOM
Salt Lake City, Utah 84132

(Roster continued on the next page.)

ROSTER (continued):

TEMPORARY VOTING MEMBERS (continued):

N. FRANKLIN ADKINSON, M.D.
Professor of Medicine
Johns Hopkins Asthma and Allergy Center
5501 Hopkins Bayview Circle
Baltimore, Maryland 21224

LESLIE HENDELES, Pharm.D.
Professor of Pharmacy and Pediatrics
University of Florida
1600 S.W. Archer Road, Room PG-05
Gainesville, Florida 32610

MICHAEL SCHATZ, M.D.
Chief, Allergy Department
Southern California Permanente Medical Group
7060 Claremont Mesa Boulevard
San Diego, California 92111

(Roster continued on the next page.)

ROSTER (continued):

FDA PARTICIPANTS (NON-VOTING):

CURTIS ROSEBRAUGH, M.D.
Director, Office of Drug Evaluation II
CDER/FDA

BADRUL CHOWDHURY, M.D., Ph.D.
Director, Division of Pulmonary and Allergy Drug Products
CDER/FDA

THOMAS PERMUTT, Ph.D.
Director, Division of Biometrics II
CDER/FDA

SALLY SEYMOUR, M.D.
Deputy Director for Safety
Division of Pulmonary and Allergy Drug Products
CDER/FDA

(Roster continued on the next page.)

ROSTER (continued):

FDA PARTICIPANTS (NON-VOTING):

SUSAN LIMB, M.D.
Medical Officer
Division of Pulmonary and Allergy Drug Products
CDER/FDA

DONGMEI LIU, Ph.D.
Statistical Reviewer
Office of Biostatistics
CDER/FDA

AGENDA

The committee will discuss biologic license application (BLA) 125277, KALBITOR, ecallantide injection by Dyax, Corp., for the treatment of acute attacks of hereditary angioedema.

8:30 a.m. Call to Order and Introduction of Committee
William Calhoun, M.D., Acting Chair

Conflict of Interest Statement
Kristine Khuc, Pharm.D., Designated Federal Official, PADAC

8:45 a.m. Opening Remarks
Badrul Chowdhury, M.D., Director, Division of Pulmonary and Allergy Products, CDER, FDA

Sponsor Presentation
(Agenda continued on the next page.)

AGENDA (continued):

9:00 a.m. Introduction and Overview
William Pullman, M.D., Ph.D., Executive Vice President of Clinical Development and Medical Affairs, Dyax Corp.

Clinical Efficacy and Safety
Patrick Horn, M.D., Ph.D., Vice President of Clinical Development and Medical Affairs, Dyax Corp.

Safe-Use Conditions
William Pullman, M,D., Ph.D., Executive Vice President of Clinical Development and Medical Affairs, Dyax Corp.

Clinical Perspective
Marc Riedl, M.D., M.S., Clinical Immunology and Allergy, UCLA David Geffen School of Medicine

(Agenda continued on the next page.)

AGENDA (continued):

Concluding Remarks
William Pullman, M.D., Ph.D., Executive Vice President of Clinical Development and Medical Affairs, Dyax Corp.

10:00 a.m. Questions for clarification

10:15 a.m. Break

FDA Presentation

10:30 a.m. Clinical Overview of the Efficacy of Ecallantide for the Treatment of Acute Attacks of Hereditary Angioedema
Susan Limb, M.D., Medical Officer, Division of Pulmonary and Allergy Products, CDER, FDA

(Agenda continued on the next page.)

AGENDA (continued):

Statistical Considerations
Dongmei Liu, Ph.D., Statistical Reviewer,
Office of Biostatistics, CDER, FDA

Clinical Overview of the Safety of Ecallantide for the Treatment of Acute Attacks of Hereditary Angioedema
Susan Limb, M.D., Medical Officer, Division of Pulmonary and Allergy Products, CDER, FDA

11:45 a.m. Questions for clarification

12:00 p.m. Lunch

1:00 p.m. Open Public Hearing

2:00 p.m. Charge and questions to Committee

Committee discussion/vote

(Agenda continued on the next page.)

AGENDA (continued):

3:45 p.m. Break

4:00 p.m. Committee discussion/vote

5:00 p.m. Adjournment

INDEX

(Index continued on the next page.)

INDEX (continued):

(Index continued on the next page.)

INDEX (continued):

PROCEEDINGS

- - - - -

DR. CALHOUN: Good morning. Welcome to the FDA Pulmonary-Allergy Drug Advisory Committee meeting.

My name is Bill Calhoun. I'm Professor and Vice Chairman of Medicine at the University of Texas in Galveston. In a minute, we're going to introduce the panel members to you.

Just to finish my own introduction, my own personal training is in pulmonary diseases and in allergy and clinical immunology.

With that, I'd like to begin by introducing the panel members, having you introduce yourself by name, affiliations, expertise, et cetera, et cetera, and perhaps we'll start with Dr. Hubbard.

DR. HUBBARD: My name is Richard Hubbard. I'm a pulmonary physician by training, received my training at Mount Sinai Hospital in New York, spent several years at the NIH. I'm the industry representative for the Pulmonary-Allergy Advisory

Committee, and I'm with Pfizer.

DR. HOIDAL: My name is John Hoidal. I'm also a pulmonologist at the University of Utah, where I'm professor and chair of the Department of Medicine. My research expertise is in the pathobiochemistry of lung injury.

DR. GRUCHALLA: I'm Rebecca Gruchalla. I'm an allergist/immunologist, professor and division chief at UT Southwestern Medical Center in Dallas.

DR. TERRY: My name is Peter Terry. I'm Professor of Medicine at Johns Hopkins. My research interests have been in pulmonary physiology and I have a degree in bioethics, also.

DR. BORISH: Larry Borish. I'm a professor at the University of Virginia and my research interest is asthma.

DR. CARVALHO: I'm Paula Carvalho. I'm a Professor of Medicine at the University of Washington in pulmonary diseases and my research interest is the bronchial circulation.

DR. HENDELES: I'm Leslie Hendeles. I'm

a clinical pharmacist at the University of Florida in the Pediatric Pulmonary Clinic, and my research interest is the clinical pharmacology of drugs for asthma and allergy.

DR. CALHOUN: Dr. Adkinson is not yet here. We'll have him introduce himself when he gets here.

DR. KHUC: I'm Kristine Khuc, the designated federal official for this committee.

DR. SCHATZ: I'm Michael Schatz. I'm Chief of the Department of Allergy at Kaiser Permanente San Diego and my research interest has been largely asthma as well.

DR. BALLOW: Mark Ballow, Women's and Children's Hospital in Buffalo, SUNY Buffalo, and I'm in the Allergy/Immunology Division. My research interest is actually immunology.

DR. HONSINGER: I'm Richard Honsinger. I'm a clinical professor at the University of New Mexico. I practice internal medicine, allergy and immunology in Los Alamos, New Mexico.

DR. FOGGS: I'm Michael Foggs and I'm

Chief of Allergy and Immunology for Advocate Health Care in Chicago, Illinois. My research interest is high risk urban asthmatics and managed care.

DR. PROSCHAN: I'm Michael Proschan. I'm a statistician at the National Institute of Allergy and Infectious Diseases.

DR. LIU: I'm Dongmei Liu, statistical reviewer at FDA.

DR. PERMUTT: Tom Permutt, Director of the Division of Biometrics II.

DR. LIMB: Susan Limb, medical reviewer in the Division of Pulmonary and Allergy Products.

DR. SEYMOUR: Sally Seymour, Deputy Director for Safety in the Division of Pulmonary and Allergy Products, FDA.

DR. CHOWDHURY: I'm Badrul Chowdhury. I'm the Director, Division of Pulmonary and Allergy Products, FDA.

DR. ROSEBRAUGH: Curt Rosebraugh, Director, Office of Drug Evaluation II.

DR. CALHOUN: Okay, thank you. Just some

mechanicals. Make sure that when you speak, firstly, that you use the microphone, the right-hand button, and turn your microphone off when you're finished your remarks. Apparently, only four channels can be open at any one time, so we don't want to talk over each other.

There is a statement that I need to read into the record this morning.

For topics such as those being discussed at today's meeting, 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 discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair.

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 the advisory committee members take care that their conversations about the 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, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

I'd like to remind everyone to please silence your cell phones and other electronic devices, if you have not already done so. The committee is reminded to refrain from discussing the meeting topics during breaks or lunch.

Thank you.

At this point, we'll have a conflict of interest statement by Kristine Khuc.

DR. KHUC: The Food and Drug Administration is convening today's meeting of the Pulmonary-Allergy Drug 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 on 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 USC Section 208, and Section 712 of the Federal Food, Drug and Cosmetic Act, are 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 USC 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.

Under Section 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts, when necessary, to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this committee have 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 USC Section 208, their employers.

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

Today's agenda involves Biologic License Application 125277, Kalbitor, ecallantide injection, by Dyax Corp. for the proposed indication of treatment of acute attacks of

hereditary angioedema. This is a particular matters meeting during which specific matters related to ecallantide injection will be discussed.

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

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusions will be noted for the record.

FDA encourages all other participants to advise the committee of any financial

relationships that they may have with any of the firms at issue.

At this moment, I'd also like to identify the FDA press contact, Ms. Karen Riley. If you're here, please stand. She may be here momentarily.

Thank you.

DR. CALHOUN: Okay. Thank you.

For the committee members, as you have need to speak, please raise your hand and signal. Kristine Khuc will develop a list and we'll simply follow the order of comments.

The only exception to that would be if there's a point of order; get my attention and we'll try to do that. But otherwise, we're going to try not to speak over each other and work through the comments in order.

With that, we'll now proceed with the FDA opening remarks by Dr. Chowdhury.

DR. CHOWDHURY: Good morning. Honorable Chairperson and members of the Pulmonary-Allergy Drugs Advisory Committee, representatives from Dyax Corporation, and others in the audience, I

welcome you to this meeting on behalf of the U.S. Food and Drug Administration.

In this brief presentation, I will introduce the objective of this advisory committee meeting and the questions that you will discuss and vote upon later in the day.

The objective of this meeting is to discuss the biological license application submitted to the agency by Dyax Corporation for ecallantide for the treatment of acute attacks of hereditary angioedema.

Hereditary angioedema is a rare disease, characterized by intermittent and unpredictable attacks of subcutaneous and submucosal edema of various parts of the body, such as face, upper airways, gastrointestinal tract, extremities, and genitalia.

The treatment options of hereditary angioedema can be considered in three categories; first, chronic long-term prophylaxis; second, short-term prophylaxis to prevent acute attacks; and, third, treatment of acute attacks.

The treatment options of hereditary angioedema are limited. In the United States, androgenic steroids, such as danazol and stanozolol, and a recombinant C1 inhibitor, are approved for short-term and long-term prophylaxis treatment. There are no drug products approved for the treatment of acute attacks of hereditary angioedema.

Ecallantide, proposed as a treatment of acute attacks of hereditary angioedema, is a recombinant 60 amino acid inhibitor of plasma kallikrein. The product is proposed to be administered as a 30 milligram subcutaneous injection by health care providers in health care settings.

As you can see on the agenda, we will start off by presentations by the applicant, followed by presentations by the FDA reviewers.

There are three major issues that I would like to draw your attention as you hear these presentations; first, the robustness of the results of the two Phase 3 efficacy studies;

second, the immunogenicity of the product and the relatively high frequency of anaphylaxis seen in the clinical program; third, the number of pediatric patients studied and the overall adequacy of the data in pediatric patients younger than 18 years of age.

Dear members of the committee, as you hear the presentations, I request that you keep in mind the questions that you will discuss and vote later in the day. I will go over the questions now.

There are a total of five questions. Questions 1 and 5 are nonvoting. Questions 2, 3 and 4 are voting questions. I will show the five questions in subsequent slides. I will not read the whole questions because they are available in print at this meeting.

Here is Question 1. This is a nonvoting question. This question is on the major safety issue that we have identified, which is Type I hypersensitivity reaction, specifically anaphylaxis. We are asking you to discuss and

provide recommendation to the agency on this safety issue.

Here is Question 2. This is a voting question. This question is on efficacy. Note that the question is broken down by age so that you can consider data in each age category as you vote.

Here is question number 3. This is also a voting question. This question is on safety. Note that this question is also broken down by age so that you can consider the data in each age category as you vote.

Here is Question 4. This is also a voting question. This question is about your approvability recommendation for this drug to the agency. Note that unlike the previous two questions, this question is not broken down by age because the applicant's proposed indication includes ages 10 years and older.

This question is based on the applicant's proposed indication and age included in the indication.

You may comment about different ages after you vote and we will take these comments into consideration.

Here is question number 5. This is a nonvoting question. In this question, we are asking your recommendation on issues such as labeling, risk mitigation strategies for anaphylaxis, potential for ecallantide being self-administered by patients outside health care delivery, et cetera.

We look forward to an interesting meeting. I thank you again for your time, effort and commitment to this important public service.

Thank you.

DR. CALHOUN: Okay. At this time, we will proceed with the sponsor's presentations.

DR. PULLMAN: Thank you and good morning. I'm Bill Pullman, Executive Vice President and Chief Development Officer for Dyax. And our purpose today is to provide you with the clinical justification that supports our BLA application seeking approval for the treatment of acute

attacks of hereditary angioedema, or HAE.

I'd be remiss if I didn't take the opportunity to thank the HAE patient community and their physicians for the support and guidance they've provided us throughout the development program, and we look forward to the dialogue with the committee today.

Here is our agenda for today's presentation. I'll provide an overview of hereditary angioedema, the physiology of the kallikrein-bradykinin pathway, the mechanism of action for ecallantide, and an overview of our clinical development program, including the development of instruments to assess treatment effect.

Dr. Pat Horn will then provide an overview of the efficacy and safety data from our Phase 3 HAE trials.

I will return to provide an overview of our proposed plan to ensure safe use. And Dr. Marc Riedl, an investigator in the clinical development program for ecallantide, will provide

a clinical perspective on the data presented today. And finally, I will return by way of conclusion and to answer questions from the committee.

As many of you know, hereditary angioedema is a rare, but very serious and potentially life-threatening disease characterized by intermittent acute attacks. HAE is inherited as an autosomal dominant trait, leading to deficiency of C1 esterase inhibitor activity.

And it's estimated that as many as 10,000 individuals in the U.S. have HAE, but less than half of them have been properly diagnosed.

Hereditary angioedema is not linked to race or gender. However, women tend to experience more attacks. Attacks and symptoms most often begin in childhood. Hereditary angioedema is characterized by severe debilitating attacks that occur spontaneously or may be triggered by stress, trauma, injury or surgery.

Attacks are unpredictable and may involve nearly any region of the body, but most notably

affect the larynx, the oropharynx, face, gastrointestinal mucosa, limbs and genitalia.

It's important to note that these attacks can begin at one or more sites and attack progression can change in severity with the course of development of the attack and additional sites become involved. Attacks can last up to five days and occur with highly variable frequency.

Laryngeal attacks are the most dangerous and they can be life-threatening if the swelling obstructs the airway, as shown here in the x-ray image, on the right. Laryngeal attacks require hospitalization, ICU monitoring, and may require intubation or emergency tracheotomy.

Without medical intervention, laryngeal attacks have been associated with 30 to 40 percent mortality and at least 50 percent of HAE patients will experience one or more laryngeal attacks during their lifetime.

Abdominal attacks are frequently of such severity that patients cannot eat for at least 48 hours due to the nausea, the vomiting and the

diarrhea as a result of the mucosal edema, as shown here.

We know from a 2006 study by Konrad Bork, which analyzed thousands of abdominal HAE attacks, that the pain is severe, with a mean pain score of at least eight on a scale of one to ten, and large fluid shifts occur with these abdominal attacks, resulting in symptomatic hypotension.

Intestinal symptoms may lead to surgery and published data suggest that as many as one-third of HAE patients have undergone unnecessary appendectomies or laparotomies. And while not life-threatening, manifestations of peripheral attacks include swelling in the face, hands and feet, and this is painful. It reduces mobility and function.

Indeed, swelling in the arms and legs can be severe enough to cause compartment syndrome, which restricts flow of blood and can lead to tissue death of the affected limb.

These attacks often have the longest duration due to the large amount of fluid

extravasation into the cutaneous tissue and the significant time necessary for the resolution of the edema.

Studies, in fact, suggest that the quicker the attack is addressed, the sooner the resolution and the better the clinical outcome. And the key to treating HAE attacks is to interrupt the kallikrein-mediated bradykinin production and prevent the attack from progressing. This allows the body to recover and appropriately redistribute the edema.

In a person who does not have HAE, critical elements of the kallikrein-bradykinin system remain in homeostatic balance, and under normal physiological conditions, the activation of plasma kallikrein and the amount of bradykinin produced is regulated by C1 esterase inhibitor, which is shown in yellow.

Conversely, when one has malfunctioning or insufficient C1 esterase inhibitor, as is the case of people with HAE, there is unrestrained activation of kallikrein and, consequently,

endogenous bradykinin release.

The body of evidence points to the critical role that kallikrein plays in the resulting excess bradykinin that's responsible for the edema, the pain and the inflammation observed in the acute attacks of HAE.

And during each attack, the already low functional C1 esterase reserves are further depleted, resulting in disregulated bradykinin release. Subsequent attacks exhibit the same pathophysiology.

Ecallantide is a novel, potent and specific inhibitor of plasma kallikrein, which was selected on the basis of high affinity and specificity for human plasma kallikrein, and it's a recombinant protein produced in Pichia pastoris.

This highly selective anti-kallikrein activity makes ecallantide an ideal treatment to reduce bradykinin, thus potentially ameliorating the signs and symptoms of an acute attack of HAE, which is highly variable in its presentation. And the intrinsic variability and presentation of

attacks have proved challenging in developing tools to reliably assess drug effect.

The ecallantide clinical program, which represents a comprehensive approach to the condition, included the development of patient-reported outcome measures, or PROs. An understanding of these measures is critical to understanding the clinical relevance of our Phase 3 data.

When the development program began, there were no validated measures for determining the severity or resolution of HAE attacks and tools available at the time measured only single endpoints, primarily related to pain.

In addition to pain, however, HAE attacks can include a wide variety and variability of symptoms which result from those abnormal edema accumulations. These include fatigue and malaise, nausea and vomiting, hoarseness, choking or difficulty breathing.

And because many of the signs and symptoms of an acute attack are only fully

appreciated and assessed by patients, a patient-reported outcome tool was essential.

Dyax worked with the agency, experts in the field and patient advocacy groups to develop meaningful and comprehensive patient-reported outcome measures.

And from our research and discussions with these groups, it was clear that an appropriate tool should capture the following: attack location, onset and evolution of symptoms, severity of all symptoms at multiple sites, and a measure of treatment effect.

And the result of these efforts was the development of two patient-reported outcome measures and I'll describe these in more detail on the next few slides.

Prior to treatment, patients were asked to specifically identify and grade the severity of symptoms at each of the five body sites, known as symptom complexes, and at specific times after treatment, they were asked to, again, rate severity of each symptom, identify new or emerging

symptoms at additional body sites, and assess response to treatment. These assessments are used to generate two scores, which I will define further.

One of the PROs was a point-in-time assessment of symptom severity, known as the mean symptom complex severity, or MSCS, score. The second PRO was the treatment outcome score, or TOS, which is an assessment in response to treatment. Both the TOS and the MSCS were developed and validated during the course of the development program.

Now, let's take a look at how these are scored.

When scoring the MSCS, patients were asked to grade the severity of each symptom complex using the following definitions for each attack location. A normal rating, which was assigned a value of zero, meant there were no symptoms at a particular location.

Mild symptoms were given a value of one and these symptoms were noticeable, but did not

affect the patients' daily activities.

Moderate symptoms were rated a two and these symptoms affect patients' daily activities and would normally cause a patient to seek treatment from a physician.

Severe symptoms, which are rated a three, were those that prevented daily activities and where treatment by a physician is required.

Let's look at an example of how these are scored.

If the patient were to present for treatment with severe laryngeal symptoms, moderate cutaneous symptoms and mild abdominal symptoms, the following scores would be assigned and the MSCS score at baseline would be the average of the three symptom sites, in this case, a score of two.

We would then take these assessments at four hours, when the symptoms would be reassessed, and compute the average at four hours. The change in MSCS would be the difference between the score at four hours and the baseline score. A negative score represents an improvement.

Putting these numbers into context, it's clear that a one-point change in the MSCS can be quite significant for an individual patient. This patient's laryngeal symptoms went from severe to mild and their abdominal pain went from mild to normal.

By utilizing imputation methods, as appropriate, we can also account for emerging symptoms occurring in this timeframe.

To reiterate, then, the MSCS score is the change in average symptom severity at a point in time.

So let's take a look now at how we assessed the treatment outcome using the TOS.

For this measure, patients were asked to rate their response to therapy for each symptom complex at key time points, for example, at four hours and 24 hours.

And for each time point, they were asked how they were feeling for each symptom complex that they experienced compared to how they felt before treatment, and the patient had three

initial choices; better, same or worse. If they answered worse, they were asked a little worse or a lot worse; and, if they answered better, they were asked a little better or a lot better.

So TOS reflecting response to treatment or intervention is a composite score of each symptom complex weighted by severity at baseline and scores range from minus 100 to positive 100, with positive scores indicating improvement.

Now that I've described the PRO measures, let's turn to the clinical development program.

The development plan followed a learning-then-confirming paradigm. Four Phase 1 studies were conducted using both IV and subcutaneous doses of ecallantide.

EDEMA0 and EDEMA1 were conducted in HAE patients and used IV dosing. In EDEMA2, the 30 milligram subcutaneous dose was first studied in HAE patients. This early program provided the basis for patient-reported outcome development and dose selection.

EDEMA3, double-blind, was a

placebo-controlled study designed to evaluate the safety and efficacy of 30 milligram subcutaneous ecallantide in patients with acute attacks of HAE. EDEMA3 also included an open-label repeat dose pod, referred to as EDEMA3-RD.

EDEMA4 was the key Phase 3 study, conducted under special protocol assessment agreement with the agency. It was a randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of ecallantide in patients with acute attacks of HAE, and patients were treated with 30 milligrams ecallantide or placebo in a one-to-one randomization.

We continue to study patients with HAE in an open-label continuation study to provide patients with ecallantide treatment for acute attacks of HAE and to gain further experience.

In the completed studies that enrolled HAE patients, 219 patients received 609 doses of ecallantide and, of these, 25 were aged 10 through 17, who were treated for 79 acute episodes. Beyond our BLA, open-labeled continuation trial

has treated over 100 patients with over 300 attack treatments.

Let's put these numbers into context. Based on gene frequency, there are an estimated 10,000 individuals with HAE in the U.S. and current estimates of those diagnosed and seeking medical treatment are around 5,000 people.

Given these statistics, the ecallantide clinical development program represents approximately four percent of patients seeking treatment in the United States, which is significantly more than clinical programs for broader indications.

With this background information in mind, I'll invite Dr. Horn to review the efficacy and safety data of ecallantide.

DR. HORN: As Dr. Pullman mentioned, we'd like to review the key measures of efficacy and safety for ecallantide. From an efficacy standpoint, we'll discuss the data from our two Phase 3 clinical trials, EDEMA3 and EDEMA4. In both trials, the primary endpoint was treatment

effect at four hours, as measured by the patient-reported MSCS and TOS.

We also studied time to response, durability of response, and additional measures of clinical impact within a single acute attack, such as the need for medical interventions and the emergence of new symptoms following treatment. Additionally, we measured the effectiveness of ecallantide therapy in patients who received multiple treatments.

We'll start by reviewing the study designs of the Phase 3 studies.

EDEMA3 was a Phase 3 randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of ecallantide versus placebo in patients with acute attacks of HAE. Seventy-two patients were randomized to either a 30 milligram subcutaneous dose of ecallantide or to placebo. Data was collected throughout the first four hours and again at 24 hours.

The primary endpoint was TOS at four hours. A change from baseline in MSCS at four

hours was a secondary endpoint. The primary analysis for EDEMA3 included eight imputations for medical interventions and two imputations for emerging symptoms, as described in the briefing book.

As mentioned earlier, EDEMA3 was a Phase 3 randomized, double-blind, placebo-controlled study designed under special protocol assessment agreement with the FDA and designed to evaluate the safety and efficacy of ecallantide versus placebo in patients with acute attacks of HAE.

Ninety-six patients were randomized to either a 30 milligram subcutaneous dose of ecallantide or to placebo. Data was collected throughout the first four hours and again at 24 hours.

The primary endpoint was the change of MSCS at four hours compared to baseline. TOS at four hours was a secondary endpoint. The primary analysis in the EDEMA4 study was performed on unimputed data.

As you can see, the trial designs are

similar, allowing for a pooling of data for further post hoc analyses, some of which we will review here today.

Based on the demographics for the EDEMA4 study, we see that the treatment groups were well matched. When we look at how the patients were randomized within EDEMA4, we see that there were more patients in the ecallantide group who had peripheral attacks and fewer patients who had abdominal attacks as compared to placebo.

Peripheral attacks, in general, are more difficult to treat and take longer to resolve. Therefore, any bias would favor the placebo group.

With respect to gender, 77 percent of subjects in the ecallantide group were female, while 58 percent in the placebo group were female.

We have performed a subpopulation analysis in the integrated dataset of EDEMA3 and EDEMA4 which showed that there was no gender-specific response to ecallantide. The relative imbalance in gender distribution in this study is unlikely to have skewed the results.

Examining the EDEMA3 demographics, we see that the study arm and the placebo arm are well matched, except for the distribution of subjects with laryngeal attacks, more of whom were in the ecallantide group. Most importantly, the demographics for both studies are representative of the HAE population seeking care.

First, we'll review data from both trials for the primary endpoint, response at four hours, using the patient-reported outcome, MSCS and TOS.

In EDEMA4, the median baseline severity was 2.0 for the ecallantide group and the same for the placebo group. Recalling from Dr. Pullman's description of MSCS, a negative value indicates an improvement in symptoms.

The median change is minus 1.0 in the ecallantide group and it is zero in the placebo group. The change in MSCS score in the ecallantide group is statistically significantly better compared to placebo.

It is important to note that since the baseline MSCS was 2.0, the median change

represents a 50 percent reduction of symptom severity, which is also seen if we look at the mean change.

Likewise, in EDEMA3, we see a median change of minus 1.0 in the ecallantide group versus minus 0.4 in the placebo group. The difference is also statistically significant and the change from baseline in the ecallantide group, again, represents a 50 percent reduction of symptom severity.

The observed treatment effect, defined as mean change in the ecallantide group minus mean change in the placebo group, is the same in both studies.

As noted earlier, the TOS is a score that can range from minus 100 to 100. A score of positive 100 would be the maximum improvement.

Here, we see that in EDEMA4, the ecallantide group median score was 50 compared to zero in the placebo group. EDEMA3 had the same median changes. The change compared to placebo in both trials was statistically significant.

Another way to look at the four-hour data is to compare the responder rates in the ecallantide group and the placebo groups. This was done using the increased number of patients in the integrated Phase 3 dataset.

I'd like to point out at this time that there were 25 patients treated in both EDEMA3 and EDEMA4. For these 25 patients, we have used their first exposure in the integrated analysis to maintain independent samples.

The results for the analyses using various values for the change in MSCS at four hours are shown here. The value of 0.3 is the MID, or minimally important difference, determined during the validation process and this is in line with the FDA's determination that a value of 0.4 is a clinically meaningful difference.

As the required change in MSCS is increased, indicating a stricter definition of responder, fewer patients in each group are considered responders. But the number of responders in the ecallantide group is always

statistically significantly greater than in the placebo group. Similar results were obtained with the TOS responder analysis.

Now, let's take a look at the data we have on the time course of symptom relief produced by ecallantide.

One metric that was evaluated was the time to onset of sustained improvement. This is defined as the first time that a patient reported feeling better and the improvement was maintained for at least 45 minutes.

Kaplan-Meier methods were used to look at the time to onset of sustained improvement. And 68.6 percent of patients achieved onset of sustained improvement by four hours in the ecallantide group compared to 41.1 percent of placebo patients.

The curves for the two groups are significantly different, with ecallantide performing better than placebo. The curves start to diverge early and difference is substantial by approximately 70 minutes, with more than 50

percent of patients in the ecallantide group reporting onset of sustained improvement in less than two hours.

For these analyses, the combined Phase 3 datasets were used. Similar analyses were performed on the individual study datasets. The data for all analyses trended in this same direction, but due to the smaller numbers in the individual studies, statistical significance was not consistently achieved.

Another question we wanted to answer was, "Does the symptom relief produced by ecallantide last?" In the trial designs, there were predefined endpoints of MSCS and TOS at 24 hours.

If we look at the symptom severity at 24 hours for EDEMA4, in the ecallantide group, we see that the median was minus 1.6. Recall that it was minus 1.0 at four hours, which shows that the patients continued to improve between four and 24 hours.

The change in MSCS at 24 hours for the ecallantide group is both clinically meaningful

and statistically significantly better than for the placebo group. The trends observed in EDEMA3 were similar, although statistical significance was not achieved. These data demonstrate that the clinically relevant response to ecallantide is maintained through 24 hours.

Let's look at the treatment outcome score at one, two, three, four and 24 hours for the combined EDEMA3 and EDEMA4 trials.

Here, the mean TOS scores for the ecallantide group are shown by the yellow bars and white for placebo. The placebo response is consistent during the initial four hours after treatment. The ecallantide response, however, increases at each time point and are statistically significantly better than placebo at all points measured after one hour.

At 24 hours, the mean TOS was 75.5 out of a possible 100. Importantly, there is no decrease in the mean score at any time point through 24 hours. The individual studies had similar statistically significant results.

Here, we do see an increase in placebo response at 24 hours, but this is expected because placebo patients in this study were not untreated patients. They were brought into a clinical setting, treated with IV fluids, and given other medications, as needed, after four hours, which would help explain the increased response at 24 hours.

We have also analyzed the Phase 3 data by attack locations, emerging symptoms, proportions of patients receiving medical interventions, and proportions of patients with substantial improvement.

The analyses by anatomic location were performed in the integrated dataset without imputation. There were 23 patients with abdominal attacks treated with ecallantide and 39 patients treated with placebo. Data at four hours is significantly better for ecallantide compared to placebo for both PRO measures.

For laryngeal attacks, where the numbers are much smaller, the change in MSCS for the

ecallantide group is better than placebo and the TOS is statistically significantly better.

Looking at the peripheral attacks, the decrease in symptom severity and the response to treatment are better in the ecallantide group than in the placebo group. Peripheral attacks are difficult to treat and slow to resolve, so it is encouraging to see improvement on both measures at four hours with statistical significance achieved for TOS.

As we have heard, the anatomic sites affected during an acute attack of HAE and the related symptom can change as the attack progresses. We've looked at symptoms that emerge following treatment with study drug in the Phase 3 studies.

Here, we see that only three patients treated with ecallantide developed new symptoms. Ten patients receiving placebo treatment developed new symptoms, including four patients who developed laryngeal symptoms.

These observations indicate that

ecallantide is more effective than placebo in stopping attack progression. They also reinforce the need to treat acute attacks at all anatomic locations in order to prevent the development of new laryngeal symptoms.

Another measure of therapeutic response is the need for additional medications. In this analysis, medical intervention includes all medications that could affect patient-reported outcomes, including open-label rescue treatments with ecallantide.

In both EDEMA4 and EDEMA3, more patients in the placebo group than in the ecallantide group required additional medication. The need for less medication in the ecallantide group is indicative of a substantial overall clinical response.

We have also investigated responses in attacks of various severities. In this analysis, we stratify the integrated Phase 3 population by baseline MSCS score. A change in MSCS of minus one indicates a full step improvement, severe to moderate or moderate to mild. So a change of at

least this magnitude was considered, in this analysis, a substantial change.

Here, we see that patients in the ecallantide group were more likely to have a change in MSCS at minus one as the baseline severity increased. We also see that patients treated with ecallantide are more likely to have a substantial improvement than those treated with placebo.

For example, in the second line, we see that 67 percent of the ecallantide patients with a baseline score of between two and three experienced greater than a one-point improvement at four hours compared to 47 percent of placebo patients. This analysis shows that the treatment effect of ecallantide is present regardless of baseline attack severity.

The data we have reviewed so far has focused on the treatment of single acute attacks of HAE. As we have heard, HAE is a disease characterized by intermittent attack; yet, the underlying pathophysiology of each attack is the

same.

So kallikrein blockade will continue to be an effective therapy. But an important clinical question is, "Can ecallantide produce a significantly positive response across multiple subsequent attacks?"

A repeated treatment analysis was conducted to assess the retention of therapeutic effect after repeated use or exposure using data pooled from the EDEMA3 and EDEMA4 studies.

Exposure to ecallantide for patients in the repeated treatment analysis is summarized by number of treated episodes. Ninety-two patients received their first treatment in EDEMA3 or EDEMA4 and 19 patients received ecallantide for five or more treatments. A combined total of 244 treatment episodes are included in this analysis.

The magnitude of the change in MSCS is consistent across all treatment episodes. A similar analysis for TOS also shows a consistently positive response to treatment across all episodes.

HAE is an orphan disease and when working with small datasets, questions in data robustness arise. We'll now examine the two Phase 3 studies and areas of potential interest.

After the start of EDEMA4, a retrospective analysis of the EDEMA3 results was completed, indicating the need to increase sample size. The EDEMA4 study was not unblinded and the power calculation was performed using only EDEMA3 data.

Importantly, there was no change to inclusion or exclusion criteria nor was there any change to study conduct, including patient recruitment, site training, or data collection methods.

To confirm that patients enrolled, pre and post sample size increase were comparable, a post hoc analysis from the initial group of patients, and the final group of patients was performed. Because of the sample size, variability in patient demographics can be expected.

Overall, the demographics between the two groups were similar. The minor differences are unlikely to have had a significant impact on response to treatment. With regard to attack locations, there are more laryngeal attacks in the latter part of the study.

We have examined responses between these two groups of patients and found an imbalance in the distribution of attack locations and responses within the treatment arms of the pre and post sample size increase groups.

The first two columns of data here compare attack site locations pre and post sample size increase for the ecallantide patients. The last two columns compare attack site locations pre and post sample size increase for the placebo patients.

Here, we see that the post sample size increase placebo group had relatively fewer abdominal attacks. For the placebo patients with an abdominal attack or a peripheral attack, the response to treatment was substantially better for

those who enrolled early in the study compared to those who enrolled later in the study.

For the ecallantide patients with a peripheral attack, the response to treatment was somewhat better for those who enrolled later in the study compared to those who enrolled early in the study.

While we can't explain these observations, there is no evidence for any systematic difference in the pre and post sample size increase groups and there is no evidence that any change in study conduct could account for these findings.

Another issue we investigated further was the impact of the medication error in EDEMA3. The data from the study are reported in the briefing book for both the as randomized and as treated populations. Because of the small sample size, the switch affects statistically significance.

Looking at the impact to the change of MSCS or TOS measures as a result of the switch or by excluding the two patients from the analysis, a

consistent treatment effect is seen in all populations.

The original analysis was performed with the per protocol Wilcoxon rank sum test without blocking for primary attack location. This analysis presumes that all attack locations respond similarly, which we have seen is not the case. The randomization for the study was performed by blocking for both primary attack location and prior exposure to ecallantide.

When the study results are reanalyzed using the more efficient and more appropriate Wilcoxon rank sum test, blocked by primary attack location and prior ecallantide exposure, as designed for the randomization strata, the results for both the as treated and the as randomized population are, in fact, statistically significant.

To facilitate direct comparison between the different populations, we performed post hoc analysis using the statistical analysis agreed to in the EDEMA4 special protocol assessment for all

groups.

This slide presents the statistical analysis of the EDEMA4 study by total population and by the pre and post sample size increase groups, as well as the EDEMA3 study, as randomized and as treated.

The decrease in MSCS in the ecallantide patients is always greater than the placebo patients. These results are clinically meaningful and statistically significant for all groups, except when the first 52 patients of EDEMA4 are examined in isolation. Similarly, for TOS at four hours, a consistent positive treatment effect is seen across all groups.

Within the constraints of small sample sizes, this is a robust dataset, demonstrating significantly greater effects of ecallantide compared to placebo for symptom relief at four hours.

It is our opinion, based upon these data, that both studies, EDEMA4 and EDEMA3, have positive outcomes. This is strengthened by

support from the secondary endpoints and consistency across all studies.

One area for consideration today is the use of ecallantide in the pediatric population. In the clinical development program, in HAE patients, the study criteria allowed for enrollment of children 10 years old and older. As previously mentioned, hereditary angioedema most often begins in childhood, with milder symptoms that significantly worsen after puberty.

While the double-blind pediatric efficacy data is limited, a total of 79 acute attacks of HAE had been treated with ecallantide in 25 patients less than 18 years of age. Eight of these moderate or severe attacks have included laryngeal symptoms.

For pediatric patients, the underlying pathophysiology of acute attacks of HAE is the same as in adults; namely, disregulated plasma kallikrein leading to increased bradykinin production.

There is no reason to think that

inhibition of plasma kallikrein will not be effective in stopping acute attacks of HAE in pediatric patients. This is demonstrated by the results from the clinical experience in patients under 18.

In this analysis, we looked at seven of the 25 patients treated in the program who received both ecallantide and placebo at various times during the clinical development program. Of these seven patients, five, or 71 percent, had a better response on ecallantide, one had a response similar to placebo, and one had a better response to placebo.

With respect to safety in this population, it is important to note that the primary route of clearance of ecallantide is by renal excretion, followed by tubular absorption and catabolism. Renal function is well established in patients by the age of 10 and doesn't differ significantly from patients aged 18 and over.

In addition, given the short half-life of

approximately two hours, there is no accumulation. There is no physiologic reason to believe that the safety profile for ecallantide will differ between pediatric and adult patients and, in fact, this is what we have found in our clinical development program.

The AE profile for the pediatric patients was, in general, similar to that of adults. There were three treatment emergent serious adverse events in the under 18 populations. These were coded as sneezing, rhinnorrhea and congestion, an adverse drug reaction, and pancreatitis in a patient with severe abdominal HAE.

We have presented multiple analyses for your consideration, all of which support the clinical efficacy of ecallantide. However, the most clinically relevant features of an effective treatment are quick response, durable response, and repeated response for multiple doses.

Based on the efficacy data from our clinical trial program, as evidenced by our primary endpoints, we see that ecallantide

produces a clinically relevant and statistically significant improvement by four hours, and more than half of patients reported onset of sustained improvement in less than two hours after receiving treatment.

In addition, the data show that the response is durable. The clinically relevant and statistically significant improvement was maintained through 24 hours. We also reviewed data that indicate that the response to treatment is maintained with multiple doses, critical for this disease with intermittent recurring attacks.

Now, let's take a look at the safety data for ecallantide.

In our evaluation of the safety data, we looked at two populations, the double-blind population and all patients treated with ecallantide.

The double-blind population included 100 patients treated with ecallantide for a total of 125 doses. The HAE patient population of 219 patients received a total of 609 doses.

Because patients were allowed to enroll in multiple studies, it was necessary to take in all adverse events across the entire development program. Therefore, adverse events are counted per patient and across all episodes.

For example, a patient who is treated 10 times is counted as one patient, but all adverse events, by preferred term, in all 10 exposures are counted.

Looking at the treatment emergent adverse events occurring in the double-blind, placebo-controlled population, we see that the number of patients reporting adverse events was similar between the ecallantide and placebo arms of the study. AEs reported in excess of five percent were limited to nausea and headache and most were reported as mild or moderate.

In the last two columns on this table, we compare the adverse events in the all HAE group to the adverse events in the double-blind clinical trials. We see a higher rate of adverse events compared to that observed in the double-blind

studies.

This is partially due to the fact that these populations received several treatments. Importantly, when we review the severity of these AEs, most were mild or moderate.

On the next two slides, we will look at serious adverse events that were determined to be treatment emergent.

In the double-blind studies, there were three treatment emergent serious adverse events in the ecallantide group and three in the placebo group. All of these were hospitalizations for HAE attacks and all were considered by the investigator to be unrelated to study drug.

If we look at the preferred terms in the all HAE population of 219 patients, there have been a total of 26 patients reported treatment emergent serious adverse events in the ecallantide clinical development program and 14 of these serious adverse events were coded as hereditary angioedema. Other serious adverse events are infrequent.

Highlighted in blue are the potential cases of hypersensitivity. Hypersensitivity is the adverse event of greatest concern.

In an attempt to fully understand the observed reactions, Dyax defined a systematic approach to reviewing adverse events to identify possible hypersensitivity symptoms from all HAE studies. This approach is outlined in the briefing book.

As part of the thorough review, we went back and examined adverse events that were reported within 24 hours of dosing using preferred terms that might suggest symptoms of hypersensitivity. Twenty-four cases were evaluated.

Following medical review of each of these 24 cases, Dyax identified 13 as possible hypersensitivity reactions, and these include the four serious adverse events previously noted.

The FDA has included two additional cases of possible hypersensitivity in their assessment. These were throat irritation and erythema. Of

these possible hypersensitivity reactions, Dyax has identified four cases as anaphylaxis and the agency has included four additional cases as potential anaphylaxis. I will review these cases in more detail.

These are the four cases that were identified by Dyax as anaphylaxis based upon the presentation of generalized symptoms which require treatment with epinephrine or other standard therapies for anaphylaxis. All of these patients had a history of allergies and three of the four reported previous allergic reactions to other medications.

It is noteworthy that all these reactions occurred within 10 minutes of the ecallantide exposure. None of the patients required intubation and all recovered without sequelae.

Two of the four patients underwent a two-phased re-challenge procedure, including a skin test, followed by a test dose of ecallantide. One patient had a negative skin test, tolerated a re-challenge dose, and has gone on to receive

numerous therapeutic doses of ecallantide with no further hypersensitivity episodes.

The four patients identified by the agency as potential anaphylaxis, which had been considered as hypersensitivity reactions by Dyax, are shown here. These reactions have all occurred following the first exposure and all with IV dosing.

All patients had a history of allergies. One patient had a negative skin test and no reaction to ecallantide on re-challenge. Two patients had negative skin tests, but symptoms recurred at the time of the re-challenge dose. One patient was not retested.

We have also examined the occurrence of potential hypersensitivity symptoms by episode in the 14 patients who were treated for at least eight episodes. In this analysis, adverse events within each episode are captured and reported independently.

We can see that the occurrence of these events is scattered across all treatment episodes

and there is no increase in the latter episodes. For a given patient, the occurrence of an event is inconsistent.

For example, the patient who experienced urticaria in episode three was treated for five subsequent episodes without reporting urticaria or any of the other hypersensitivity symptoms. This raises a question of whether or not this case of urticaria truly represents a hypersensitivity symptom to ecallantide.

Next, we'll review the ecallantide immunogenicity data. Among the 219 ecallantide-treated HAE patients, 13 percent of the patients developed anti-ecallantide antibodies. Two percent of the patients have developed anti-ecallantide IgE antibodies and eight percent of the patients have developed IgE antibody to the host cell yeast Pichia pastoris.

In the Phase 3 studies in which the samples were assayed for neutralizing antibodies, 1.6 percent of patients developed neutralizing antibodies to ecallantide in the in vitro assay.

We have looked at the safety and the efficacy in these patients with antibodies. It is important to note that none of the patients who developed any of the antibodies, including neutralizing antibodies, have shown a drop-off in efficacy.

In addition, patients who developed antibodies to ecallantide did not show an increase in overall AEs when compared to patients who did not develop antibodies.

There is no one-to-one correlation between the presence of antibodies and hypersensitivity reaction. However, it should be noted that three of the patients with possible anaphylaxis had antibodies to ecallantide or P. pastoris.

In summary, ecallantide appears to be safe and is well tolerated. AEs were similar to placebo and the majority were mild to moderate. There were no serious adverse events in the double-blind studies, other than hospitalizations due to HAE.

Of the 15 patients who have experienced hypersensitivity reactions, there were four cases classified by Dyax as anaphylaxis. The proportion of patients reporting any adverse events was similar, regardless of the presence or absence of anti-ecallantide antibodies.

Dyax has monitored both hypersensitivity and immunogenicity carefully throughout the development program and, as you will hear now, if approved, we will continue to monitor patients to ensure safe use of ecallantide.

Dr. Pullman will now discuss this topic in more detail.

DR. PULLMAN: Thank you, Dr. Horn.

As Dr. Horn has just concluded, based on accumulated data, ecallantide has a favorable tolerability profile. However, there have been cases of hypersensitivity, and for this reason, we're developing a program to ensure safe use of ecallantide with the following goals in mind.

First and foremost, we'll restrict self-administration. Ecallantide will be limited

to administration by a health care professional in a medical setting.

In addition, we want to collect more information on patient use, hypersensitivity, and to identify potential prognostic factors to help address the risk of hypersensitivity.

Furthermore, we'll educate patients and their physicians on ecallantide and the identification and treatment of anaphylaxis, including the use of re-challenge procedures. Thus, our overall aim of this plan is to monitor ecallantide use and to ensure that it is used safely, under controlled conditions.

We've given these goals considerable thought and would like to present a real world example of how a physician and specialty pharmacy will work together to benefit the patient.

Let's start with a patient diagnosed with HAE. Once a patient is identified, the physician will enroll in the program, send the prescription to the centralized specialty pharmacy, and enroll the patient in the product registry.

The physician, who has consulted with the patient, will notify the specialty pharmacy regarding the best administration locations for future treatments and the pharmacy will ship ecallantide to these sites, as well as the appropriate educational materials to the patient and treatment physicians.

For patients, materials include education on recognition and treatment of hypersensitivity and anaphylaxis, access to a patient-focused Website, and to a toll-free help line.

Health care providers will receive product information and materials on recognizing and treating hypersensitivity. They'll also have access to a health care provider specialized Website and a toll-free help line.

Once a patient has an attack, they would go to one of the predetermined locations for administration of ecallantide treatment. This would enable 24/7 supervised access for the patient. As part of the registry, we'll collect demographic information, type and severity of

attack, treatment response, and any adverse events, including hypersensitivity reactions.

In the event of a hypersensitivity reaction, the patient will be appropriately treated in this medical setting for this reaction. The physician will notify the specialty pharmacy, who will put shipments on hold and notify the backup treatment centers that future treatment for that patient is suspended.

However, at the prescribing physician's discretion, a re-challenge procedure could be performed. If the patient agrees to and passes re-challenge successfully, the specialty pharmacy will refill the prescription and remove the treatment hold. If the patient fails the re-challenge procedure, they will not be allowed further treatment with ecallantide.

With this program in mind, I'd like to ask Dr. Riedl to come to the lectern to share his perspective on treating patients with HAE and with ecallantide.

DR. RIEDL: Mr. Chairman and members of

the advisory committee, thank you for the opportunity to speak with you today.

I've been treating patients with HAE for the past eight years. I've been involved in HAE clinical research and publications, including EDEMA4, which was presented here today.

I've worked closely with the United States Hereditary Angioedema Association, the leading patient support organization for HAE. As a matter of disclosure, I have a contract with Dyax for my services as an investigator and consultant.

It is my belief that the physical, social, psychological and financial impact of HAE on patient lives cannot be overstated. I'm talking to you today as both an investigator and a clinician, because I believe that ecallantide is an important treatment for patients with this disease.

Today, there is no product approved for the treatment of acute HAE attacks in the U.S., so there's a critical need for a treatment such as

ecallantide that can effectively interrupt the bradykinin pathway and help resolve an HAE attack.

With the lack of effective FDA-approved acute therapy products, treatment of HAE has focused on the chronic administration of prophylactic medications.

While these may lessen the number of attacks, there's extensive evidence that prophylactic care is insufficient to completely prevent attacks, leaving patients with a need for a medication that can reliably halt HAE attack progression, lessen severity, and lead to sooner recovery.

The data from EDEMA3 and EDEMA4 highlight the needed important clinical benefits I see in my practice. We saw that ecallantide patients with laryngeal attacks were five times more likely to get swelling relief within four hours.

In clinical practice, this directly relates to reduced respiratory complications, reduced patient anxiety, and how quickly a patient can leave the hospital.

For abdominal attacks, we saw that twice as many ecallantide patients had onset of pain relief within four hours. In my experience, this relief leads to reduced emergency room visits, hospitalizations, and use of narcotics and antiemetics.

As a reference, there are about 15,000 known emergency room visits annually for acute HAE attacks. Reducing the progression of peripheral attacks can reduce overall attack duration so patients can resume their normal lives and activities. It's been reported that HAE patients lose up to 100 days of school and work a year due to acute attacks.

Finally, fewer ecallantide patients had progression to new emerging sites, lessening the morbidity and duration of acute attacks. Yet, the clearest examples of ecallantide's clinical effect come from the open-label extension studies.

For example, I care for a patient who suffered two separate laryngeal attacks that were halted with ecallantide, allowing her to return

home in excellent condition within four hours.

That same patient had a third subsequent laryngeal attack, but was too far from our center to receive treatment with ecallantide. As a result, she was hospitalized for nearly two weeks, requiring a tracheotomy and then a later support.

Other patients tell me that the relief that ecallantide provides from an abdominal HAE attack represents the difference between returning to home or work within a few hours instead of spending the day in the emergency room or hospital.

Granted, this is open-label experience, but these observations help us better understand the key findings from EDEMA3 and EDEMA4.

It's also important to note that the early intervention of HAE attacks results in earlier symptom control and more rapid recovery. By halting the progression of symptoms, ecallantide expedites the resolution of HAE attacks.

Thus, patients regain their normal lives

and functioning within hours rather than days, and severe outcomes, such as surgery and asphyxiation, are avoided.

As an HAE specialist, I'd like to share my perspective on the hypersensitivity and anaphylaxis issue with ecallantide.

I find that HAE patients are thoughtful and do carefully weigh the risks of therapy. It's my experience that patients will choose to use ecallantide knowing the risks of hypersensitivity and anaphylaxis. This decision is supported by two primary factors.

First, HAE patients are very familiar with their symptoms. They, along with their treatment specialists, will be able to distinguish HAE from hypersensitivity reactions. For example, compared to anaphylaxis, HAE symptoms evolve more gradually, without urticaria and pruritis.

Second, patients receiving ecallantide will be treated by medical specialists with intimate knowledge of HAE and anaphylaxis. As you know, it often takes several years for a patient

to be properly diagnosed by a specialist, usually, allergists/immunologists and some acute care physicians. These specialists are well versed to recognize and effectively treat acute hypersensitivity reactions, should they occur.

Furthermore, the safe use program that Dyax has outlined will ensure that treating physicians and their patients are aware of ecallantide efficacy and safety, including recognition and management of hypersensitivity reactions.

So although we can't eliminate the risk, we can effectively manage this risk. Given the enormous burden of HAE on patient lives and the benefits of ecallantide, it's my belief that HAE patients will actively seek access to ecallantide.

Perhaps the most important message I can convey to you is what ecallantide means to my patients. Approximately 70 percent of my HAE patients have entered into placebo-controlled HAE trials, seeking a solution for acute attacks. This speaks to the severity and life-altering

nature of this disease.

Patients are very interested in ecallantide because it can reduce the impact of an HAE attack. As further support of the benefit to patients, all of my patients that have participated in ecallantide trials have asked to remain in the open-label extensions.

These patients consistently report that the medication gets them back to their everyday life within hours rather than the two to five days typical of an untreated HAE attack.

I cannot emphasize enough that HAE attacks are not simply a nuisance, but have a tremendous impact on physical and psychological functioning. Overall, my patients clearly see the benefits of ecallantide over the risk of hypersensitivity reactions, supporting the importance of ecallantide in addressing an unmet medical need.

On behalf of HAE patients and caregivers, I thank you for your time and I look forward to a thoughtful clinical discussion on ecallantide.

DR. PULLMAN: Thank you, Dr. Riedl.

We'd like to acknowledge that this committee is accustomed to seeing much larger clinical trial databases. However, rarely does a product for an orphan indication such as ecallantide offer much data.

Based on the efficacy data from our clinical trial program, we see that, for many patients, ecallantide is an effective solution. It produces a clinically relevant and statistically significant improvement by four hours.

In addition, the data show that the response is durable, with robust improvement maintained through 24 hours, resulting in continued suppression of the attack.

We also showed data indicating that the response to treatment is maintained with multiple doses over time, critical for this disease with intermittent recurring attacks.

Importantly, ecallantide is well tolerated. Adverse events were similar to placebo

and the majority were mild to moderate. However, hypersensitivity and anaphylaxis is an identified risk. Our safe use program and the fact that ecallantide will be administered under medical supervision provides an environment for managing the risk of hypersensitivity and anaphylaxis.

Dyax is committed to ensuring that patients have rapid access to ecallantide so that acute attacks of HAE can be treated quickly, while having appropriate controls in place to ensure safe use.

Fortunately, HAE is rare. Unfortunately, without treatments that block the mediators of the attack, patients will continue to needlessly suffer. We believe that the ecallantide efficacy and safety data, coupled with our proposed safe use program, supports approval of ecallantide for the treatment of acute attacks of HAE.

Thank you for the opportunity to present our data to you today and we look forward to answering your questions.

DR. CALHOUN: Okay. Thank you to the

sponsors for their presentations.

One point of business before we move on to our question and discussion period.

Dr. Adkinson is here.

Frank, could you introduce yourself?

DR. ADKINSON: Good morning. My name is Franklin Adkinson. I'm from the Johns Hopkins Asthma and Allergy Center in Baltimore and I bring to the panel an interest in and experience with drug hypersensitivity problems.

DR. CALHOUN: Okay. Thank you.

This set of presentations is open for the discussion by the panel.

Dr. Ballow?

DR. BALLOW: I know there's going to be a lot of questions about the adverse events and the anaphylaxis. But before we get into that, I wanted to go over slide C52 again.

There was a lot of data presented and maybe I didn't catch this, but what was the summary here, that the patients that were treated early on did not have as good a response as the

patients that were treated in the latter part of EDEMA4?

Is that what I heard? Is that what this slide says?

DR. HORN: One of the issues is that EDEMA -- there was a sample size increase in EDEMA4 and that increase initially pre-specified at 52 patients and then the sample size increase increased it to 96.

When you look at the total E4, EDEMA4, which is in the first column, the 96, those are the results there. When you split that out and just look at the first part of the study and the second part of the study, there's a difference in the results in terms of the treatment effect seen.

However, the treatment effect is always in the same direction and always favors ecallantide over placebo.

DR. BALLOW: Well, the column under, first, 52, though, the change was very small.

DR. HORN: The change is very small.

DR. BALLOW: It's .09 with a P value that

was not significant, right?

DR. HORN: Right.

DR. BALLOW: So what's the take on that? Was it the same lot? Was it a different lot, a drug?

DR. HORN: So when we see a difference like this, a question comes up as to why is the first half of the study different than the second half of the study, and that's where we went back and looked and looked at study conduct.

There was no change in study conduct. There was no change in drug supplied. There was no change in the groups of patients that enrolled pre and post. So we could not find a reason that the two groups would respond differently.

DR. BALLOW: So it was the same lot of drug.

DR. HORN: Same lot of drugs.

DR. BALLOW: Okay. Strange.

DR. CALHOUN: I'm going to take chairman's prerogative here, because the questions I want to ask really go to the fundamental outcome

variables, the mean symptom complex severity and the treatment outcome score.

You mentioned that they had been validated. And the question, of course, then, is how were they validated, in that there is no gold standard.

And I've got a couple of specific questions regarding the spacing of the scores. It would seem to me that a score from zero to one means something pretty different than a score from one to two, and the score from two to three probably doesn't mean as much as the differences of score from one to two.

The second piece of that is that the site of affection, cutaneous versus abdominal versus laryngeal, probably are not, in fact, all of equal importance and, yet, in the scale, they are given equal weighting.

So I'd like you to maybe discuss that a little bit.

DR. HORN: So multiple questions. So your first question was on the validation process.

So these patient-reported outcomes were validated as a longitudinal program over the clinical development program for ecallantide. So they started out in the very early studies with some of the PRO design.

They had cognitive debriefing following the information obtained in EDEMA3 and then the data was actually validated in the complete validation package in the EDEMA3 study.

This validation process was in compliance with the FDA's guidance for PRO validation and all of the validation has been submitted as an evidence dossier as part of the BLA filing for ecallantide.

Now, you have to remind me of the follow-up questions.

DR. CALHOUN: So the other questions related to the magnitude of importance in the difference between a score of zero, a score of one, a score of two, and a score of three, because based on the descriptive information there, it looks to be that that scale is completely

nonlinear, that there are big steps and there are small steps.

So I'd like you to discuss what the implication of that might be, particularly with respect to patients who have different degrees of baseline symptoms.

DR. HORN: So in order to be enrolled in the clinical studies, a patient had to have an attack that was identified as moderate or severe. So they had to have at least one symptom complex that had a baseline severity score of two or three.

They could have had additional symptom complexes with others, including mild symptom complexes, which would, in fact, change the baseline severity.

We have done a complete analysis by symptom location and by severity to look at the changes of MSCS and how they could have impacted it.

We can address that in the question-and-answer session or we can address that

now. We have some backup slides for that, if you want to see that, or you want to hold that off to the questions and answers.

DR. CALHOUN: In the question and answer later on, we can do that.

DR. HORN: Okay. But the short answer to your question is there is no impact of either initial symptom complex, location or severity in the overall -- there isn't one overall symptom complex or one severity that drives the MSCS and TOS to any more extent than the other.

DR. CALHOUN: Thank you.

Dr. Schatz?

DR. SCHATZ: I had really a similar question and I realize there's a lot of details on the validation, but it is so central to the efficacy issue. I guess I'd be curious to ask one question.

What was used as the gold standard for the validation?

DR. HORN: So in a disease state like this where there is no gold standard, where there

is no validated, as we collected the information, at the same time points that the information was collected, patients were asked an overall question.

They were asked, "Overall, how are you feeling compared to how you felt before baseline," and then that was what the changes in the MSCS -- so their change on that and that was scored the same as the TOS, with a little -- significantly worse to significantly better, with a five-point scale, and then that was the anchor for basing the MSCS and TOS changes on.

DR. CALHOUN: Dr. Hoidal?

DR. HOIDAL: I think you've addressed some of my question related to the pre and post and the EDEMA4. But can you take that a little further? Were there new sites involved, new investigators involved that hadn't been involved or more so in the -- or a different age in the subjects? Because that difference is striking.

DR. HORN: So we looked at what we could find. Throughout the EDEMA studies, continuously,

new sites were being enrolled. After the first 52 patients were dosed, there were a total of 44 total sites in the EDEMA study.

Nine of those -- I believe 11 sites came on board after the dosing of the 53rd patient, but nine of the patients were treated at new sites; the remaining 35 were treated at preexisting sites.

DR. HOIDAL: And did those nine distinguish themselves in any way from the rest of the group?

DR. HORN: Those nine were not among the group of patients identified as having an MSCS that differentiated them from the others.

DR. CALHOUN: Dr. Hubbard?

DR. HUBBARD: Yes. I had a question also about the validation and the assessment of the patients.

At any time, was a simple physician's global assessment done of these patients?

DR. HORN: The physician did an assessment at the primary time points, at baseline

and at four hours. The physician did an assessment based on symptom severity. He ranked the patients' symptoms. He ranked the response, he or she, and he or she also did an overall assessment, as well, as part of the PRO validation.

DR. HUBBARD: And was that data captured?

DR. HORN: That data was captured. That data is not shown because there is a very, very tight correlation between that and patients.

DR. HUBBARD: Okay.

Then my other question was about this additional assessment for the patients done prior to and after the protocol amendment.

I'm just wondering why you did that. Were you asked to do that? That's not a typical post hoc analysis.

DR. HORN: The EDEMA4 study was performed, as we said, under a special protocol assessment agreement with the FDA. So that when we -- in the amendment, then also had to be approved to maintain the agreement.

So as part of the amendment and increased sample size, we were asked to perform this analysis.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: Just a few points. As I look at your MSCS data, it's really weighted toward cutaneous reactions; that is, it looks like we're looking at three different cutaneous sites, is that right, that we're looking at to get to the -- when you pick up five different scores for your MSCS, three of those are cutaneous.

Only one is abdominal and one is laryngeal, if I'm right. So it would weight it that way.

I wonder, as you did the study, if patients were allowed to treat at all with a prodrug; that is, some of these patients can tell you when they're going to have an angioedema attack and I think that this drug should be more effective if given at the onset of the attack than waiting until the edema occurs.

I would wonder, as you watched your

patients in the later phase of the study, you have patients that have been on that study, you have investigators that are now more enthused about a drug, if you were treating your patients earlier in the latter part of EDEMA4.

DR. HORN: So in these Phase 3 studies, the inclusion criteria mandated that the patient have moderate or severe attacks. So to be enrolled, they needed to have at least one symptom complex that was moderate or severe. So that's the data here.

DR. CALHOUN: Dr. Proschan?

DR. PROSCHAN: I think I know the answer. I just want to make sure.

So this change, for example, in MSCS, this is only in those areas in which there was a problem at baseline. You don't look at the places where there was no problem, unless there -- you talked about -- well, first of all, let me see if that's correct.

DR. HORN: In the EDEMA4 analysis, unimputed data, that is correct.

DR. PROSCHAN: Okay. So I just wanted to follow that up, because the imputed analysis, if someone gets a problem in a new location, say, at two hours, then, as I understand it, you assigned them a zero, a normal score at baseline, and then you assigned them the score at the point where they had that new problem or is it four hours after that?

DR. HORN: So in the imputed analysis, which would be the sensitivity analysis for EDEMA4, that is the case. So if they had an emerging symptom at four hours, that actual symptom severity is captured and then the symptom complex is imputed into the baseline as a zero.

DR. PROSCHAN: But if they had it at two hours, then do you look at that person at six hours? How do you --

DR. HORN: No. So if they only had it at two hours or -- I guess I'm not understanding quite your question.

DR. PROSCHAN: Okay. Suppose they had an emerging problem at two hours in a different

location that was not the baseline, was not identified at baseline. Then you impute a normal score at baseline. And then do you look at them four hours later or you just say, "Okay, we're going to impute their four-hour score to be whatever their severity was at that second hour?"

DR. HORN: Their four-hour data is their actual data.

DR. PROSCHAN: Okay.

DR. CALHOUN: Dr. Gruchalla?

DR. GRUCHALLA: I have a hypersensitivity question, but if we want to stay focused on this issue right now, would you like me to wait? Okay.

Regarding the sensitization -- what I mean, sensitization, the formation of IgE antibodies -- this was determined by in vitro testing, correct, not skin testing? I mean, I know skin testing was done, but that was more prior to a challenge.

DR. HORN: Right. So the antibody assays were in vitro assays.

DR. GRUCHALLA: Okay. And I don't know

if I read this correctly. So only two percent developed the anti-ecallantide antibody, IgE?

DR. HORN: Yes.

DR. GRUCHALLA: And that's after how many administrations of the drug?

DR. HORN: That depends on how many they had. So it's two percent of the overall population. So some of those have had one exposure, some of had two, some have had up to 25 in our development program.

DR. GRUCHALLA: Okay. But as they go up, did that percentage increase? Have you looked at the subpopulations?

DR. HORN: There is a little bit and we have a seroconversion curve. Again, we can hold it for QRAs or we can take a look at that now.

DR. GRUCHALLA: The only thing that concerns me is just the sensitivity of the assay -- well, actually, sensitivity and specificity of the assay. As we all know, this is a fairly small molecule. I don't know if it's multivalent and all this. I mean, Franklin, I

think, could be better at this than I can.
But just my question about sensitivity. Are we missing people that may have potential IgE?
DR. HORN: I'll let Dr. Pullman address the assay.
DR. GRUCHALLA: Okay.
DR. PULLMAN: The only thing I can add to that question is we are having conversations and dialogue with the agency on that very question, matrix effects and sensitivity, to ensure that the assay sensitivities are appropriate.
What I can say is the assays went through a full validation procedure, but we are engaged in discussions on that topic.
DR. GRUCHALLA: Okay.
DR. CALHOUN: Dr. Carvalho?
DR. CARVALHO: I have two questions. First of all, was there any objective data gathered rather than just symptom progression and the patients' grading scales? Were there any hemodynamic parameters obtained or flow volume loops, actual edema measurements during the study?

DR. PULLMAN: No, there were not. But we did measure blood pressure over the course of the attack episode and it shows what you might expect. There's some relative hypertension in both placebo and ecallantide groups and no significant difference between the two.
But we did not employ any other form of pharmacodynamic marker in the EDEMA3/EDEMA4 program with respect to kallikrein, C4 levels, et cetera.
DR. CARVALHO: And I have a second question, if I may. I'm curious.
Looking at the data, was there any site change with repeated treatments? In other words, were people more likely to have laryngeal symptoms later, abdominal symptoms later, peripheral, as patients were treated over time?
DR. PULLMAN: There was no pattern, as we expect, unpredictable and wide variety of attack locations presented, so no consistent systematic pattern for any particular patient or population.
DR. CARVALHO: Thank you.

DR. CALHOUN: Dr. Hendeles?
DR. HENDELES: I have a few questions. One relates to the risk of a Type I statistical error. It seems like the same data got analyzed several times in several different ways and I'm just wondering whether you took into account that and made adjustments for it in the statistical analysis.
The second question is, are there any excipients in the formulation other than the active drug that could account for the allergic reaction.
The third question -- would you like me to stop and you answer it?
DR. PULLMAN: That might be best. Thank you. I got the first two, I believe.
DR. HENDELES: Okay, go ahead.
DR. PULLMAN: So risk of Type I errors in the analyses. There were no multiple adjustments necessary in the E4 or the E3 settings for the primary endpoints, so none were applied.
But in the integrated dataset, to ensure

independency, we only counted patients on their first exposure, which is why, if there were 168 patients between the two, the 143 is presented. So we've only counted them on one occasion, so that we've reduced that chance of lack of independence.
With respect to excipients, there is host cell protein in the drug substance and drug product. The host cell protein is actually at a low level. It's at eight parts per million, which is below the most stringent threshold of 10.
In the early part of the process, which actually applied to EDEMA0, 1 and 2, this was the clinical trial material supplied for intravenous, levels of host cell proteins were higher, about 70-fold higher.
Based on that, we actually introduced an additional step in the manufacturing process, an anion exchange step, reduced it 70-fold, brought it well within industry accepted acceptance criteria for host cell protein. But that is the one that is there.

DR. HENDELES: Regarding your plan for safe administration, I didn't notice any mention of epinephrine being prescribed for the patient and taught how to use it once they left the administration site. And secondly, what did you have in mind for locations at night and weekends?

DR. PULLMAN: If I can perhaps answer the question in reverse order. It's a medically-supported environment.

So it could be emergency room, emergency care centers, physicians' offices, if they are open after hours, clearly; so all of that is intended for the discussion between the physician and the patient to say where -- "If I get an attack in the early hours of the morning, where can I go to be medically supervised for that?"

Under the medical supervision component of this, then, and, clearly, in our educational materials, we'll provide whatever additional education in terms of both identifying and managing hypersensitivity.

We've given the epinephrine, for example

the EpiPen, thought, but under the control and restriction, no self-administration. We felt that that was not warranted. But it is warranted in a medical administration with an observation period, and I think that's the key element here.

DR. CALHOUN: Dr. Foggs?

DR. FOGGS: With regard to the EDEMA4 pre and post sample size, do you have any data concerning the proportion of patients that had a partial response, that is, recurrence of symptoms within a 24-hour period, for each respective group?

Secondly, the argument has been made that because there is substantial evidence, according to the presenter, that the efficacy of the treatment would be the same in the pediatric population, the question is, by extrapolation, why are you only asking for an indication for age 10? Why are not you asking for an indication substantially below age 10?

DR. PULLMAN: Perhaps I'll answer the pediatric question and ask Dr. Horn to address the

earlier question of the 44 versus 52 with respect to 24 hours and responses.

No, we're requesting an indication for 10 and above based on the data we presented. We have no experience below the age of 10. In fact, I think one would argue that pharmacokinetic experience to ensure the adequacy of dose bridging, if that's appropriate, would be needed.

In the 10 through 18, just on that topic, we do have data from our population PK collected from 19 pediatric subjects, to indicate that the exposure is similar to adults, that there are no covariates of age and weight, but that's over the age of 10. So that's what we're talking about here for the pediatric population.

DR. CALHOUN: Dr. Borish?

DR. PULLMAN: Did you want me to come back and answer or try and address the 44 to 52 question on responders or do you want to leave that for later?

DR. CALHOUN: Sorry. Yes.

DR. HORN: So could you just clarify the

question for me, please?

DR. FOGGS: The question is for each respective group in the pre and post sample size change, what was the proportion of patients that had a partial response, that is, recurrence of symptoms within 24 hours after administration of the treatment?

DR. HORN: So we haven't specifically looked at the pre and post sample size group for that. But what we have found is in the entire development program, that very few individual patients have had a return of symptoms. It's in the single digits across the entire development program, but we have not specifically looked at the first 52, second 44, for EDEMA4.

DR. FOGGS: That may be of some clinical relevance because of the gross discrepancy between the P values between each respective group.

DR. HORN: But the P value is on the primary endpoint, which was at the four-hour determination.

DR. FOGGS: I understand that, but still,

from an empiric standpoint, since the data is weak in some respects, I think that would be important.

DR. HORN: Okay.

DR. CALHOUN: Now, Dr. Borish?

DR. BORISH: Thank you.

To some extent, based on how we think this disease acts, I'm surprised the efficacy rate isn't 100 percent. And I suppose one explanation is that once edema is allowed to develop, you may be shutting the barn door, but that certainly doesn't explain why new symptoms are so often developing after administration of the drug.

So two specific questions. One is, I couldn't find in any of the source documents any data regarding time from onset of the episode to administration of the drug as a function of efficacy. I know with lots of the HAE drugs, you really have to give it quickly. So I don't know if that kind of a retrospective analysis was done.

The second question is in regard to the 30 milligram dose. I saw lots of PK data, but I'm curious whether you know that at that 30 milligram

dose, to what extent are you blocking kallikrein and to what extent are you blocking kallikrein diffusely in all of the relevant tissue and what is the duration of that comprehensive blockade in the tissue?

DR. HORN: Okay. So a fair number of questions and the first was --

DR. BORISH: The first was the -- the second was, I guess, the blockage question, but the first was a retrospective analysis, time to onset of symptoms to administration of the drug as a function of efficacy. You have to give it quickly.

DR. HORN: So we, in fact, looked at that and in our inclusion criteria it was within eight hours. We did go back and do a retrospective analysis, and let's call the slide up.

This is the median change in MSCS score at four hours by time from onset of symptoms in the integrated Phase 3 analysis. So in this analysis, there were a total of 10 patients treated in the zero to two-hour group, six in the

ecallantide group, which is yellow, and four in the placebo group, which is white.

And in the two to four-hour period, there were a total of 46 patients, 21 in the ecallantide group, 25 in the placebo, and on down through the four to six and six to eight hours. And from this information, it does seem that the response is lessened after six to eight hours.

DR. BORISH: Okay. And the second question, are you sure 30 milligrams is the right dose? It's a short version of the second question.

DR. HORN: So we have the inhibition slide that has ecallantide and C1 inhibitor for the inhibition.

Slide up, please.

So in this slide then, the open circles represent the inhibition of plasma kallikrein by ecallantide and the closed circles are by C1 inhibitor, and it's a comparison.

Our plasma levels we get -- our Cmax plasma levels we get with ecallantide are about 85

nanomolar. So at that dose, there is a hundred percent inhibition of plasma kallikrein.

Now, granted, you're comparing in vitro and in vivo, but from our best estimate, that at the 30 milligram dose, we are clear over about the hundreds, so well -- 100 percent inhibition of the first curve.

DR. BORISH: You never looked at tissue concentrations, whether that could be an issue, especially like in an edematous GI tract.

DR. HORN: No.

DR. BORISH: Well, that was a rhetorical question, but a specific question might be in an edematous hand, where you actually could get tissue concentrations.

DR. HORN: But, again, ecallantide does not inhibit tissue kallikrein. It only inhibits plasma kallikrein, which is thought to be the mediator of HAE. So we didn't look, no.

DR. CALHOUN: Okay. Because of the constraints of time, we're going to limit our discussion to what has occurred so far. There

will be time later in the meeting for additional questions and discussion of both the sponsor's presentations and the FDA's presentations.

At this point, we're going to take a 13-minute break. It's 10:17 by my watch. We will convene promptly at 10:30.

Just a reminder to the panel members, remember that there should be no discussion of the issues during the break amongst yourselves or with any member of the audience.

(A recess was taken.)

DR. CALHOUN: Okay. Good morning, again, folks. If I can have your attention, we're going to move on with the FDA presentation at this point. So we'll begin with the clinical overview of the efficacy of ecallantide for the treatment of acute attacks of hereditary angioedema by Dr. Limb.

DR. LIMB: Good morning. My name is Susan Limb and I am the FDA medical officer in the Division of Pulmonary and Allergy Products. Today I will be discussing the findings of the agency's

clinical review for ecallantide, which is proposed for the treatment of acute attacks of hereditary angioedema in patients 10 years of age and older.

To start, I will begin with a brief background about HAE and a product description of ecallantide. I will then present an overview of the clinical development program, followed by an introduction to the efficacy analysis, focusing on study design and endpoint selection in the two pivotal studies.

After my introduction, the agency's statistical reviewer, Dr. Dongmei Liu, will speak about the efficacy analysis in more detail. Once we have completed the presentation of efficacy, I will then address the safety profile of ecallantide before concluding the agency's presentation with a summary of the clinical review's main findings.

As we heard earlier, hereditary angioedema is a rare disease estimated to affect one in 10,000 to 50,000 individuals worldwide. We've already heard how attacks can be highly

variable between individuals and within an individual.

Laryngeal attacks have life-threatening potential, but attacks at other sites also have significant morbidity.

The frequency of attacks is highly variable. Some patients will have less than one attack per year, while others may have attacks on a weekly basis.

Several studies have estimated that attack frequency is around seven to 14 days for untreated patients. The variability of attacks and even in a given individual makes HAE especially challenging to study in a clinical trial.

Currently, there are no drug products approved for the treatment of acute attacks of HAE in the U.S. The standard of care for acute attacks is supportive therapy; for example, opiates for pain management or intubation for airway obstruction.

Since angioedema is common to both HAE

and anaphylaxis, epinephrine is occasionally used for its vasocontsrictive properties in acute HAE attacks, but epinephrine's efficacy for acute attacks is limited.

Several drug products are available for prophylaxis, including several alkylated androgens, like danazol, stanozolol, oxymetholone, and oxandrolone. Please note that of these agents, only danazol, stanozolol and oxymetholone are approved in the U.S. and the latter two are no longer available.

While the literature indicates that these agents can reduce the frequency of attacks, many patients continue to have breakthrough attacks. Also, these prophylactic medications have significant side effects which limit their use.

For example, the androgens are associated with hepatotoxicity and hepatocellular adenomas. The masculinizing effects of androgens also limit their use in women and children.

Antifibrinolytic agents are not approved in the U.S. for HAE but are used elsewhere. These

drugs are associated with muscle cramps, increased creatinine kinase levels, and an increased risk of thrombosis.

Fresh-frozen plasma is occasionally used for short-term prophylaxis, but the literature suggests that its use in an acute attack may actually worsen the condition. Most recently, recombinant C1 inhibitor replacement therapy was approved in the U.S. for chronic treatment, but its efficacy in acute attacks has not been established.

The proposed indication for ecallantide is the treatment of acute attacks of HAE in patients 10 years of age and older. It is intended to be administered only by a health care professional in an appropriately monitored setting.

The data that I will be presenting today was collected under these very specific circumstances. The efficacy and safety of self-administration has not yet been studied.

Ecallantide is a new molecular entity and

a novel recombinant inhibitor of human plasma kallikrein. It was derived from human tissue factor pathway inhibitor and shares 88 percent homology with endogenous TFPI.

It is a 60 amino acid protein produced in P. pastoris yeast cells by recombinant DNA technology. Glycosylation, oxidation and N-terminal truncation can occur and leading to the formation of ecallantide-related variants that are biologically active.

Ecallantide is supplied as a colorless, preservative-free, isotonic solution for injection. The proposed dosing regimen is a 30 milligram subcutaneous dose administered as three separate one cc injections to sites away from the primary attack site.

In cases of insufficient relief or recurrence of symptoms, an additional 30 milligram dose may be administered within a 24-hour period.

The applicant conducted 11 clinical studies in HAE with ecallantide. The Phase 2 HAE program is presented in this slide. The Phase 3

studies will be presented separately in the next slide.

As expected for an orphan drug program, the size of the clinical program is limited. In addition, please note that patients were eligible to enroll in multiple sequential studies of ecallantide, so that many patients participated in several studies, including both of the Phase 3 studies.

The BLA submission was based on a total of 219 unique HAE patients who had been treated with 609 doses of ecallantide. EDEMA0 and EDEMA1 were initial proof of concept studies that evaluated single intravenous doses of ecallantide. These studies will not be presented today, but details of these studies can be found in the agency's briefing materials.

EDEMA2 was an open-label repeat dose study that provided dose ranging information for the selection of the 30 milligram subcutaneous dose. This study will be discussed in more detail shortly.

This table summarizes the Phase 3 HAE program, consisting of the two pivotal studies, EDEMA3 and EDEMA4, and the corresponding open-label extension studies, EDEMA3-RD and DX-88/19. For the purposes of this presentation, I will refer to the open-label studies as the EDEMA3 open-label study and the EDEMA4 open-label study.

The two major studies, EDEMA3 and EDEMA4, were randomized, double-blinded, placebo-controlled trials that looked at the efficacy of a single 30 milligram subcutaneous dose of ecallantide for treatment of acute HAE attacks. I will discuss the study design and efficacy variables in more detail later.

Additional efficacy and safety information on repeat dosing was collected during the open-label studies.

However, please note that the EDEMA4 open-label study remains ongoing and only limited safety information on hypersensitivity reactions were included in the original BLA. Therefore,

data to support chronic repeat dosing is based primarily on the EDEMA3 open-label experience.

In addition to the HAE patient studies, the applicant conducted four Phase 1 trials in healthy volunteers and one study for a different indication in cardiac surgery patients. The applicant also provided information from a re-challenge study in patients with hypersensitivity reactions to ecallantide, as well as compassionate use experience narratives.

Pertinent safety information from these other studies will be presented in the safety portion of this presentation. More detailed information about these studies can be found in the agency's briefing package.

With that, I would now like to turn our attention to dose selection. In general, limited dose ranging information is available for ecallantide and it is obtained primarily from the EDEMA2 study.

In this study, qualified patients presenting within four hours of onset of an acute

attack of at least moderate severity were treated with a single dose of open-label ecallantide, or dose A.

If no improvement was noted within four hours, a second dose, dose B, could be administered. Patients could receive a maximum of 20 doses for separate attacks.

Escalating intravenous doses from five to 20 milligrams per meter squared and a 30 milligram subcutaneous dose were given in sequential dose cohorts.

The 30 milligram subcutaneous dose is estimated to correspond to an intravenous dose of approximately 15 milligrams per meter squared. Patients were not restricted to a particular dose cohort and could receive subsequent doses at different levels from the one received previously.

A total of 77 unique HAE patients were treated for 240 attacks in this study. Patients ranged in age from 10 to 78 years of age and 65 percent were male. Twenty of the 77 had prior exposure to ecallantide in one of the other Phase

2 studies.

In EDEMA2, efficacy was based on patient symptom report. These symptom reports were largely descriptive and did not include a validated scoring system. In this study, a successful outcome was defined as onset of resolution within four hours of dosing and continuing for 24 hours after dosing.

As can be seen in this table, there was no clear dose response. Of the 240 treated attacks, approximately 69 percent of the attacks were reported to have a successful outcome.

Among the four dosing groups, the 30 milligram subcutaneous dose had the highest proportion of successful outcomes at 82 percent, followed by the 10 and 20 milligram per meter squared IV doses, respectively.

Based on these findings, the 30 milligram subcutaneous dose was selected for further study. While the results should be interpreted with caution due to some of the design limitations of EDEMA2, the results suggest that the selection of

the 30 milligram dose for the Phase 3 program was reasonable.

The design and conduct of the two major studies, EDEMA3 and EDEMA4, were similar. EDEMA3 included 72 patients from 25 sites in the U.S., Canada, Europe and Israel. EDEMA4 evaluated 96 patients from 30 study sites in the U.S. and Canada.

Both studies consisted of a double-blind phase, followed by an optional open-label phase, where patients could receive treatment for additional acute HAE attacks. During the double-blind phase, patients presented within eight hours of onset of symptoms of a moderate to severe attack and were randomized to receive a single 30 milligram dose or placebo.

In EDEMA3, patients were eligible to receive an additional unblinded 30 milligram dose, dose B, for severe upper airway compromise. In EDEMA4, patients were eligible for dose B both for severe upper airway compromise or recurrent persistent symptoms.

During the open-label phase of both studies, patients presenting with new HAE attacks received ecallantide 30 milligrams subcutaneously. New patients who had not participated in the double-blind phase were also eligible to enroll.

In the EDEMA3 open-label study, patients with worsening or persistent symptoms could receive a second blinded dose of ecallantide or a placebo. In EDEMA4, the second dose was unblinded dose of ecallantide.

Please note that the double-blind portions of each study were designed to assess a single dose. The clinical program did not include a placebo-controlled evaluation of repeated exposures. Efficacy and safety data to support chronic repeat dosing is based primarily on the EDEMA3 open-label experience.

Although EDEMA3 and EDEMA4 were similar in many ways, I would like to highlight two major differences in their design and conduct; one, the choice of efficacy endpoint for the primary endpoint and, two, the imputation schemes used in

the statistical analysis.

EDEMA3 used the treatment outcome score, or TOS, at four hours as the primary efficacy endpoint. The change in mean symptom complex score, or MSCS, from baseline at four hours was a secondary endpoint.

Both the TOS and MSCS are patient-reported scoring systems that were developed by the applicant specifically for use in the ecallantide clinical program.

As we heard earlier, there is no gold standard for assessing HAE attack severity or progression. The complex nature of HAE attacks makes objective measurement of symptoms difficult. Even for a given individual, attacks can vary, affecting the intra-individual retest reliability of a symptom scoring system.

With these factors in mind, I will discuss the TOS and MSCS in more detail in the upcoming slides, as these efficacy variables are complex and the clinical relevance of these measures is not entirely transparent.

Nevertheless, compared to the TOS, the agency felt that the MSCS was a more straightforward measure. As a result, the agency recommended that the order of these endpoints be reversed in the second pivotal study, EDEMA4, so that the change in MSCS from baseline was now the new primary endpoint, followed by the TOS as a key secondary endpoint.

In addition to the difference in primary endpoint selection, EDEMA3 and EDEMA4 differed in their imputation schemes. The statistical analysis plan for EDEMA3 included imputation for medical interventions and emerging symptoms as part of the pre-specified primary analysis.

While these imputations were considered to be clinically relevant, the agency was concerned that these were not conservative imputations. As a result, the agency requested that the primary analysis for EDEMA4 be conducted without imputations.

Dr. Liu, the agency's statistical reviewer, will provide a more detailed discussion

about the impact of these imputations.

Finally, in addition to the major study differences, I will mention two other issues which distinguish EDEMA3 and EDEMA4 from one another and appear to have had an impact on the efficacy results.

The first issue has to do with the dosage administration error that occurred during the conduct of EDEMA3. One patient, randomized to ecallantide, mistakenly received placebo, while a second patient, randomized to placebo, received ecallantide. This dosage administration error impacted the primary efficacy analysis and will be discussed in further detail.

While no such dosing errors were reported for EDEMA4, the protocol for EDEMA4 was amended after the study had already been initiated. The applicant increased the sample size from 52 to 96 patients.

The agency agreed to the sample size modification, provided that it was not based upon an unblinded assessment of EDEMA4 results

collected up until that time and that other aspects of the study did not change.

This amendment appears to have impacted the efficacy results of EDEMA4 and will also be discussed later in this presentation.

Moving on to the main efficacy endpoints, I will now describe the TOS, which was the primary endpoint for EDEMA3.

The TOS is a composite weighted symptom score intended to assess symptom response to treatment. Baseline severity and response to treatment are assessed by patients for five possible symptom complexes; one, internal head and neck; two, stomach, GI; three, genital/buttocks; four, external head and neck; and, five, cutaneous.

Baseline severity is scored on a scale of zero to three, normal to severe. The applicant has defined severe as a patient's condition requiring treatment due to an inability to perform activities of daily living; for example, a patient's throat being so swollen that they have

difficulty breathing or having feet swollen so that they cannot walk.

Moderate is defined as a situation where treatment is highly desirable and symptoms impact activities of daily living; for example, a patient's hands are so swollen that he or she cannot button his own shirt.

Mild symptoms are those that are noticeable, but do not impact activities of daily living and normally is the patient's baseline state, absent of an acute HAE attack.

The baseline severity is determined for each symptom complex, then multiplied by the response assessment, ranging from minus 100 to plus 100, significant worsening to significant improvement.

The sum of the individual symptom complexes is then divided by the sum of the baseline severity assessments, providing a weighted score.

The maximum and minimum possible TOS is plus 100 and minus 100, with the higher value

corresponding to greater improvement. A TOS value of zero signifies no change.

Since the TOS is a composite score, different anatomic sites may potentially cancel one another out. For example, if a patient has significant improvement of cutaneous symptoms, but significant worsening of laryngeal symptoms, the respective changes may cancel each other, so that the TOS is zero or no change.

As you can see, even with a detailed explanation of the TOS, it is difficult to interpret and the relationship between a given score value and clinical changes is not transparent. The agency has concerns that the TOS may exaggerate differences of questionable clinical relevance or, alternatively, obscure important changes.

In an effort to validate the TOS instrument, the applicant conducted cognitive debriefing interviews in angioedema patients, as well as a designated study to assess the psychometric properties of the TOS. Based on

these evaluations, the applicant has proposed a value of 30 points as the minimum clinically important difference.

Please be aware that the agency has not made a decision on whether a 30-point difference is clinically relevant or whether the validation studies support the TOS instrument. The true clinical meaning of 30 points on the TOS is up for discussion and I will return to this point during the presentation of the efficacy results.

Given the complexity of the TOS, the agency recommended that the MSCS be used as the primary variable in the second pivotal study, EDEMA4. As we heard earlier, it is calculated as the arithmetic mean of the severity assessment for the five major symptom complexes.

Unlike the TOS, there is no inherent temporal outcome element in the MSCS. The maximum possible value is 3.0 and the minimum possible value is zero. Accordingly, the greatest possible change from baseline is plus or minus three.

As shown here, this is the same severity

scale used in the calculation of the TOS. It is important to note that the MSCS and TOS are related and correlation between these two measures is expected.

While the MSCS is a more straightforward calculation, it does raise the same issues of interpretation and clinical relevance that we have for the TOS. The applicant has proposed that an MSCS difference of 0.3 points is the minimum clinically important difference.

Again, the agency has not made a decision on whether a 0.3 point difference is clinically relevant or whether the validation studies support the MSCS. We will revisit the proposed minimum clinically important difference later.

In addition to the TOS and MSCS, several other efficacy endpoints are worth highlighting. MSCS and TOS data were collected at the 24-hour post-dose time point as a reflection of durability. These data are described in more detail in the briefing package.

To get a sense of the proportion of

patients who improved in ecallantide, Dr. Liu will show results of a responder analysis using various threshold cutoff values for the TOS and the MSCS.

Time to report a significant improvement was a separate symptom score based on patients' global self-assessment. This scoring is independent of the MSCS and TOS scoring and helps provide a clinical correlation to the MSCS and TOS scores.

We will also talk about medical intervention patterns which are of particular interest, since this endpoint is independent of symptom scoring and provides an alternative clinical assessment of efficacy.

As mentioned EDEMA3 and EDEMA4 provide the main efficacy support for ecallantide. The EDEMA3 and 4 patients and their presentations appear to be consistent with typical HAE attacks described in the literature.

A total of 168 patients were included in the controlled portion of the Phase 3 studies. Some patients participated in both studies, so

there are 143 unique patients.

In both studies, the patient population was primarily female and Caucasian, with a mean age of 35 years. Both studies stratified for prior participation in an ecallantide study.

Few pediatric patients were evaluated during the controlled phase of either EDEMA3 or EDEMA4. The youngest age treated with ecallantide during the controlled double-blind phase was 16 years of age. There were additional pediatric patients down to the age of 10 years who participated in the open-label studies.

A total of 15 patients under the age of 18 years have been treated with the to-be-marketed 30 milligram subcutaneous dose. Whether this number is sufficient to draw conclusions about the efficacy and safety of ecallantide in the pediatric population will be a topic for discussion later today.

Overall, the HAE attack history and concomitant medication patterns were similar between the two studies. In EDEMA3, the most

commonly reported symptom complex of at least moderate to severe severity in the ecallantide group was divided between cutaneous and GI attacks.

In EDEMA4, cutaneous attacks predominated overall and there were fewer patients with GI attacks in the ecallantide arm compared to placebo. In both studies, laryngeal involvement of at least moderate severity was reported in about a fifth of the patients.

Dr. Liu will soon present the efficacy analysis in detail, but I will provide an overview of the main findings and highlight the major concerns that the agency has identified with the efficacy data.

This table summarizes the main efficacy results for both pivotal studies. As you can see in the leftmost column, the presentation of results is slightly different for EDEMA3 compared to EDEMA4.

Recall that EDEMA3 had a dosing administration error. The original analysis plan

only called for intention to treat, or ITT, as randomized. However, due to the dosing error, the applicant performed a post hoc analysis based on the ITT as treated population.

When comparing the two sets of results, you can see that the pre-specified as randomized results are numerically supportive but are not statistically significant.

When the analysis is adjusted for the dosage administration error, the treatment difference appears to be statistically significant. While these results generally support ecallantide's efficacy, the results of EDEMA3 are not robust and the limitations of a small sample size are apparent.

No such dosing error occurred in EDEMA4, so only intention to treat as randomized results are presented here. Looking at these results, EDEMA4 appears to have robust findings in support of ecallantide over placebo.

In this study, a treatment difference of minus 0.4 for the MSCS was observed, exceeding the

proposed minimum clinically important difference of 0.3 points. Likewise, results for the TOS calculation also favored ecallantide over placebo and exceeded the proposed minimum clinically important difference of 30 points.

However, exploratory analysis of the EDEMA4 results has raised questions about the robustness of these findings. As mentioned earlier, the applicant amended the protocol in the middle of the study to increase the sample size.

This table shows the efficacy results pre and post sample size adjustment. The results for the original 52 patients planned for EDEMA4 are not significant, while the results for the additional 44 patients are statistically significant.

It appears that the statistically significant findings for the overall study are driven primarily by these latter 44 patients. In particular, the placebo group performed appreciably worse in the latter part of the study.

When comparing the patients enrolled

before and after sample size change, there are no clear differences in demographics or baseline HAE history to explain the discrepancy. More patients in the earlier part of the study appear to have participated in other ecallantide studies, but that is not surprising.

In terms of presentation, there appear to be more severe attacks, in general, before the sample size adjustment compared to afterwards, as well as fewer laryngeal attacks. Both before and after sample size adjustment, more patients in the ecallantide group had severe attacks compared to placebo.

Conceivably, more severe attacks may be less likely to respond to ecallantide, but this pattern has not been consistently observed in the efficacy data as a whole. And when comparing the results pre and post amendment, the performance of the ecallantide group is not that different, despite differences in starting severity.

The applicant has suggested that relative differences in the primary anatomic site of attack

may have impacted these results. According to the applicant's experience, abdominal attacks tend to resolve more quickly and show larger responses at four hours in comparison to peripheral attacks.

As shown in the table, there were proportionately more placebo patients with peripheral attacks following the sample size change compared to before, although, in both parts of the study, there were still more placebo patients with GI attacks.

In addition, if we look at the most extreme patients in the dataset, there is no clearly predominant attack site.

This figure shows the change in MSCS results for individual patients plotted against the time of enrollment along the X-axis. The black dots represent placebo patients and the red dots represent ecallantide patients.

The dotted line in blue indicates the time of the sample size increase. As you can see, circled here in green, there is a group of six placebo patients treated after the protocol

amendment who clearly performed worse.

This table summarizes the characteristics of those six placebo outliers. Both male and female patients were represented and the age was close to the mean age for the total population. The patients were each recruited at a different U.S. study site.

No single anatomic attack site predominated. All of the patients required a dose B for persistence or worsening of symptoms. Some patients appeared to improve after administration of dose B, while one patient reported no improvement and the second worsened considerably, requiring hospitalization for a worsening GI attack.

Based on this look at the individual outliers, there are no clear characteristics that distinguish these six patients from the rest of the study population.

Now, all of the data that I have shown you so far was based on single dose data from the controlled phase of the EDEMA3 and EDEMA4. Before

I conclude this overview of the efficacy results, I will briefly discuss repeat use data. As mentioned earlier, data to support the efficacy of repeat dosing comes primarily from the open-label portion of EDEMA3.

This table summarizes the patient exposure during the EDEMA3 open-label study, which lasted nearly two years in duration. In addition to patients rolling over from the double-blind phase, 18 new patients were enrolled and treated. A total of 160 attacks in 66 patients were included.

As you can see, the majority of patients were treated for one additional attack during the open-label study. One patient was treated for 13 attacks.

This table summarizes the main efficacy findings for the repeat dosing open-label phase of EDEMA3 up through the sixth treatment episode. The first row of the table shows the mean TOS and MSCS results reported for the ecallantide arm during the double-blind portion of the study for

comparison.

Numerically, the TOS and MSCS values suggest that there is no apparent decline in efficacy over repeat dosing. However, keep in mind that the later values are based on fewer and fewer patients.

Given that the open-label phase lasted almost two years, one might have expected a larger number of patients presenting for repeat dosing. The patient numbers may reflect the inherent variability of the disease or may be a byproduct of study logistics.

Alternatively, there may have been some self-selection among patients who were responders versus those who were non-responders. In other words, patients who experienced a benefit from ecallantide may have continued to present for subsequent attacks, while patients with lesser responses may have chosen not to participate any further.

In summary, the limitations of the EDEMA3 data and the questionable robustness of the EDEMA4

results have been the primary issues for the agency's efficacy review of ecallantide. These results will be the focus of the discussion later this afternoon. In addition, as mentioned earlier, the pediatric data is limited and will be another issue for discussion.

With these issues highlighted, I will now turn it over to Dr. Liu, who will present a detailed look at the statistical analysis of efficacy.

DR. LIU: I'm Dongmei Liu, the statistical reviewer, and I will be presenting the efficacy result of this application.

The discussion on efficacy is split into three major parts; collective evidence on efficacy in the two Phase 3 studies, sensitivity analysis on data imputation, and then we will have some information on pediatric patients.

Before we get into a detailed discussion, I'd like to make one point clear at the beginning. In efficacy analysis, there are various ways to analyze data. Some of the analysis we did here

were different from the sponsor's analysis. What we would like to highlight is that when looking at data in different ways, the study conclusion can change.

I will start with the major issues we identified in the double-blind part of the two Phase 3 studies.

This slide is a plot to show the distribution of change of MSCS at four hours post-dose from baseline by enrollment date. The X-axis is enrollment date. The Y-axis is change of MSCS at four hours post-dose from baseline.

Each point here is a patient. Because in the double-blind phase patients only received single dose treatment, so each point here also indicates one treatment outcome. The blue square indicate patients in the ecallantide arm. Black dots indicate patients in the placebo arm.

The improvement of symptom is reflected by a reduction of MSCS. So the patients in the lower part of the plot are the ones that performed well. The patients in the upper part of the plot

were the ones who performed poorer.

An abnormal pattern we observed in the studies, that there were six placebo patients who enrolled in the later stage of the study, performed very poor and they stand out clearly as outliers.

In the next couple of slides, we'd like to explain why we are so cautious with this abnormal pattern.

Susan already showed this slide. So this is just a repeat of the information.

Toward the end of EDEMA4, the sponsor submitted a protocol amendment to require sample size increment. This was because after EDEMA3 was finished, the observed effect size in EDEMA3 was smaller than the expected effect size the sponsor used to do sample size calculation for EDEMA4.

So with the reduced effect size, the predefined -- with the reduced effect size, the predefined sample size was not big enough. The sponsor asked to increase the sample size from predefined 52 to 96.

The blue dotted line indicates when the protocol amendment was proposed. The black dotted line indicates where the population is split into two parts, the original 52 patients recruited based on the predefined sample size and the additional 44 patients recruited after the sample size increment.

We see all six patients who performed extremely poor in the placebo group are recruited after the decision of sample size increment. We also see that more patients in the ecallantide arm performed extremely well after the decision of sample size increment. This observation is very disturbing because the treatment effects were very different in the two study periods.

Based on the sponsor's presentation, Dr. Horn commented that this difference could be partially explained by the two subgroups, the placebo patients with abdominal attack and the ecallantide patients with peripheral attacks.

For placebo patients with an abdominal attack, the response to treatment was

substantially better for those who enrolled early in the study compared to those who enrolled later in the study.

Among five of the placebo outliers recruited after sample size change, three of them entered the study with abdominal attack. However, this only explains what causes the difference, but it doesn't explain why patients performed so differently before and after the sample size change, so our question still remains.

We did analysis to test if the difference between pre and post sample size adjustment is statistically significant. The result is summarized in the table. And this is the repeat information from Susan's slides, again.

The treatment difference measured by a change of MSCS is negative .09 in the original 52 patients, with a P value of .8, and it is negative .9 in the additional 44 patients recruited after sample size increment, with a P value less than .001. The treatment difference was increased 10-fold.

A similar result was observed for TOS at four hours post-dose. The treatment difference measured by TOS at four hours post-dose was 24 in the original 52 patients, with a P value of .2, and this increase to 72, with a P value of .002 in the additional 44 patients recruited after sample size increment.

The treatment difference was increased three-fold. We already said it appears that the statistically significant findings in EDEMA4 are driven primarily by the 44 patients added after protocol amendment.

To formally test if the inconsistency in treatment difference between the two study periods is statistically significant, we did logistic regression on efficacy endpoint by defining patients as responders or non-responders. The responder is defined as a patient with a change of MSCS at four hours post-dose less or equal to negative one.

The plot here shows the distribution of change of MSCS in the two arms, separated by study

period. The dotted line indicates the cutoff on MSCS to define responders.

We first checked the percentage of responders in each arm in a single study period and then checked if the difference between the two study arms in each study period is different.

This table summarizes the test result. So in the original 52 patients, there were 54 percent responders in the ecallantide arm and 46 percent responders in the placebo arm. The difference between the two arms was eight percent.

In the 44 patients added after the protocol amendment, there were 70 percent responders in the ecallantide arm and 13 percent responders in the placebo arm. The difference between the two arms was 57 percent.

Testing the difference between pre and post sample size adjustment by a logistic regression was interaction between treatment effect and the enrollment period. We get a P value of .04 on the interaction term.

The known hypothesis of the test is that

the treatment difference between the two study arms is the same in the two study periods. P value of .04 indicates that the chance to observe such inconsistency is very rare.

What we can conclude here is that the treatment difference changed substantially after sample size increment. There is no treatment difference before sample size adjustment and very large treatment difference after sample size increment. The question is which one we should believe.

That's the major issues in EDEMA4 and now we look at EDEMA3.

Dr. Limb already showed in the earlier slides that the robustness of EDEMA3 is questionable. There were two patients that accidentally received the wrong drug in EDEMA3 and two patients are enough to alter the study conclusion. It's already an indication that the EDEMA3 efficacy result is not robust.

In addition to that, since both the primary efficacy endpoints, TOS and MSCS, were

analyzed by nonparametric Wilcoxon rank sum test, there are some drawbacks of this rank sum test that concern us.

It only cares about the order of the data, but not the absolute value. So even if the difference was confirmed as statistically significant, it doesn't guarantee the difference is clinically meaningful, so we paid particular attention to responder analysis.

The responder in this analysis was defined in the same way as the plot we showed for EDEMA4. The analysis result is summarized in this table. Again, the right part of the table repeats the information in the last two slides and the left part of the table is the result for EDEMA3.

Both analyses are based on ITTS treated population. We see that in EDEMA3, there were 67 percent responders in the ecallantide arm and 53 percent responders in the placebo arm. The difference between the two arms is 14 percent.

Applying logistic regression to the responder analysis gives us a P value of .3 on

treatment difference between the two arms. In other words, although the ecallantide arm had more responders than the placebo arm, the difference is not statistically significant.

The sponsor also proposed other cutoffs on TOS and change of MSCS to define responders. This table summarizes the analysis on all proposed cutoffs.

In the earlier presentation, Dr. Horn showed a similar table of this, but that's based on data from the integrated Phase 3 study. The conclusion is that the responder analysis is significant at all cutoffs. But now let's have a look at the same analysis by study and separate it by study period in EDEMA4.

Again, we see in EDEMA3 the difference between the two study arms are all relatively small, regardless of what cutoffs applied. In EDEMA4, all large differences were detected in the additional 44 patients recruited after sample size increment.

That closes our discussion on collective

evidence, efficacy evidence in the two Phase 3 studies. Other than the major issues we just presented, there is a common problem in the primary efficacy endpoints in both studies, the data imputation on TOS and MSCS.

Dr. Proschan had a question on data imputation for emergent symptoms. In the next couple of slides, we will explain in detail how this affected the study conclusions.

This graph shows how the study was conducted. Patients entered the study at baseline, indicated by zero hour. MSCS was measured at this time point and then patients received the initial injection. After four hours, TOS and MSCS were measured again before the patient was released.

Because the calculation of TOS and MSCS is based on summation over all tiered symptom complexes, if there was a symptom complex not observed in the baseline that emerged during the study period, this will affect how TOS and MSCS is calculated.

The other one that affects the evaluation of TOS and MSCS is the rescue treatment the patient could receive after the initial injection study drug. So the treatment effect observed at four hours post-dose could be due to either the initial injection of study drug or the rescue treatment.

Data imputation is necessary to take these effects into account. There are various ways to do data imputation and how data are imputed will affect the test results on treatment difference differently. We will first present the imputation rules proposed by the sponsor, talk about its consequence, and then discuss alternative imputation rules.

Before we get into the detail of imputation rules, let's have a look at the percentage of data that are imputed in the two studies.

In EDEMA3, there was one patient in the ecallantide arm who had emergent symptoms and there were three patients in the placebo arm who

had emergent symptoms.

Four patients in the ecallantide arm in EDEMA3 received a medical intervention during the study and 14 patients in the placebo arm in EDEMA3 received a medical intervention.

In EDEMA4, the number of patients with emergent symptoms or received medical intervention almost doubled the number in EDEMA3, with one exception that there were much more patients in the ecallantide arm in EDEMA4 that required rescue treatment.

An important message here is the imbalanced percentage of data imputed in the two study arms. A consequence of this imbalance is that the imputation will have an imbalanced effect on the two study arms, too.

In this slide, we present a section of the imputation rules proposed by the sponsor and use it as an example to show how the imputation affects the study conclusions. A similar effect was observed when imputation was done for medical intervention.

So when there was an emergent symptom complex and it didn't resolve at four hours post-dose, for the imputated data, the emergent symptom complex would be included in the baseline MSCS calculation and the severity of the emergent symptom was assigned to be zero.

For the unimputed data, this emergent symptom was not included in the baseline MSCS calculation. However, the so-called unimputed data is not exactly unimputed. Because it ignored the emergent symptom in the baseline, theoretically, it is the same as assigning average MSCS to the emergent symptom for the baseline severity.

So the unimputed data were imputed, too; it's just imputed implicitly. The calculation at four hours post-dose was the same for the imputed and unimputed data.

For a single observation, this imputation rule will increase the change of MSCS at four hours post-dose. Thus, the imputed data is always greater than the unimputed data. Because there

were more data in the placebo arm that were imputed, this resulted in enlarged treatment difference between the two study arms.

To put that in a graph, this shows how the imputation rules affect the two study arms differently. The colored dots here indicate patients with emergent symptoms or received medical intervention, there are more data that need to be imputed in the placebo arm than in the ecallantide arm.

So there were more blue dots than red dots. After imputation, the colored dots are shifted upwards. Because of the imbalanced percentage of data imputed in the two study arms, the treatment difference was enlarged.

The imputation rules proposed by the sponsor were designed for a conservative measure on TOS and MSCS. However, as we showed in the last two slides, because of the imbalanced percent of data imputed, this imputation rule favored the study drug.

So we call it anticonservative imputation

rules. Alternative imputation rules that are expected to lead to conservative rules are necessary to assess the robustness of study result.

Considering there were more emergent symptoms and medical interventions in the placebo arm than in the ecallantide arm, we suggested reversing the imputation rules proposed by the sponsor and see if the same trend can be confirmed by the analysis based on data imputed according to the new rules.

We call the new rules the conservative imputation rules. The difference between the two imputation rules are highlighted in the table.

One thing we want to point out here is that both the anticonservative imputation rules and the conservative imputation rules are the extreme cases. Neither of them is reasonable in estimating treatment difference, but these imputations can provide us information in assessing the robustness of treatment difference.

This slide represents the P value of

primary efficacy analysis based on sponsor's defined unimputed data. There were four efficacy endpoints we considered here. The first two are from EDEMA3 and the last two from EDEMA4, in order of changing MSCS and TOS, both evaluated at four-hour post-dose.

All of them were tested by Wilcoxon rank sum test. The analysis is based on ITTS treated population.

The dotted line here indicates P value equal to .05. If we put the P values from the analysis based on data imputated according to the anticonservative rules, as we expected, because the treatment difference is enlarged, the result becomes more significant and P values become smaller.

If we put the P values from analysis based on data imputed according to conservative rules, we get the result in the reversing direction and, therefore, away from the significant level.

As we already talked in the previous

slides, both the anticonservative and conservative imputation rules presented here are the extreme imputation rules. They may not be reasonable in estimating treatment difference.

It is only used to provide us information in assessing how robust the treatment difference is. Because the so-called unimputed data were actually imputed, too, it's implicitly imputed. So the result based on unimputed data are not the correct estimate of true treatment difference either.

What we can tell from this plot is that the true treatment difference lies somewhere between the two extreme cases. But since the range of variation is so wide and the primary efficacy endpoint is so sensitive to data imputation, the robustness of treatment effect is in question.

That closes our discussion on data imputation and now we move on to efficacy information for pediatric patients.

Because the sponsor proposed ecallantide

for treatment in patients who are 10 years of age or older, we did subgroup analysis on age.

This table summarizes the number of pediatric patients in each study. In EDEMA4, there were two pediatric patients in the ecallantide arm and seven pediatric patients in the placebo arm.

In EDEMA4, there are two pediatric patients in the ecallantide arm and three pediatric patients in the placebo arm. The sample size of the pediatric group is too small and there is not enough evidence to confirm the efficacy in this group.

To summarize the discussion on efficacy, we conclude that efficacy results in EDEMA3 are not robust. EDEMA4 data are inconsistent before the two study periods. Primary efficacy endpoints are sensitive to data imputation and there is no sufficient efficacy result for pediatric patients.

Now, I return the presentation to Dr. Limb and move on to the discussion on safety issues.

DR. LIMB: I would like to now turn our attention to the safety evaluation for ecallantide. As mentioned before, the dose is intended to be administered by a health care professional in an appropriately monitored setting.

The safety data that I will present were collected under these circumstances. The efficacy and safety of self-administration have not yet been studied.

With that in mind, I will begin with an overview of patient exposure and the safety parameters that were assessed in the clinical development program before addressing the adverse event profile of the drug.

This portion of the presentation will focus on anaphylaxis, which is the main safety concern for ecallantide. I will then summarize the main efficacy and safety findings of the clinical review to conclude the agency's presentation this morning.

The safety database for ecallantide is

based primarily on the HAE studies, which included 219 unique HAE patients. A total of 609 doses were administered. As shown in this table, approximately half of the patients received one dose.

Eighty patients received two to four doses, nine patients received five to nine doses, and 12 patients received more than nine doses. In the controlled portion of the Phase 3 studies, 100 patients received 125 doses of ecallantide.

As mentioned in the efficacy presentation, pediatric data is limited. Twenty-five patients under the age of 18 years have received some formulation of ecallantide. Only 15 have received the 30 milligram subcutaneous dose.

Although ecallantide is not expected to behave differently in younger patients compared to adults, there is little data to confirm this assumption. Certain other subpopulations, such as patients with renal or hepatic impairment, were not specifically studied.

Safety assessments in the Phase 3 clinical trials included screening for adverse events, physical exams, vital signs, routine clinical laboratory tests, and urinalysis. Serial ECG monitoring was performed in EDEMA4 in lieu of a formal thorough QT prolongation study.

Serial antibody testing was performed for IgE and non-IgE antibodies to ecallantide and IgE antibodies to P. pastoris, the yeast medium in which the drug is produced.

A review of physical exams, vital signs, clinical parameters and ECG data did not show any clinically relevant differences between the ecallantide and placebo arms. More detailed information about these safety parameters can be found in the agency's briefing package.

As a result, I will focus on the remainder of the presentation on the adverse event data and immunogenicity data.

This table shows the adverse events that were reported in more than one patient in the Phase 3 population and that occurred more

frequently in the ecallantide group.

Overall, adverse events were reported at a similar rate in both treatment arms and there were no discontinuations due to adverse events during the controlled period. The most common adverse events associated with ecallantide were headache, nausea, diarrhea and pyrexia.

Injection site reactions were also reported more frequently in the ecallantide group and this will be discussed in more detail momentarily.

In the controlled portions of EDEMA3 and EDEMA4, HAE was the only severe adverse event reported in more than one patient and this occurred at a similar frequency between the two treatment groups. A similar adverse event profile was seen for the total HAE program, with headache, nausea, fatigue and diarrhea being reported most commonly.

The notable exceptions were an increased number of injection site reactions and several reports of anaphylaxis. I will now discuss these

particular adverse events in more detail.

In the controlled phase of the Phase 3 studies, local injection site reactions were reported in three patients in the ecallantide group compared to one patient in the placebo group. All three of the patient were seronegative for antibody to ecallantide or P. pastoris. In the total HAE population, injection site reactions were reported in six percent of patients.

The reactions were characterized primarily by pain, itching and erythema. One case of local urticaria was reported. The reactions were transient and resolved without intervention, differing from the severe local reactions that were observed in earlier animal studies with the drug.

Many of these patients went on to receive additional doses of ecallantide without further reactions. The local reactions did not seem to be predictive of more serious systemic drug reactions, like anaphylaxis or other adverse events.

As a protein therapeutic, hypersensitivity reactions to ecallantide are expected. The applicant defined anaphylaxis as a severe systemic immunologic reaction, rapid in onset, presumably caused by antibody-mediated release of vasoactive mediators from tissue mass cells and peripheral blood basophiles.

Anaphylactoid reaction was defined as an immediate nonimmunologic systemic reaction that mimics anaphylaxis but is caused by nonantibody-mediated release of mediators from mass cells and basophiles.

In an attempt to capture these events, the applicant performed a search using these MedDRA preferred terms. From this search, the applicant identified three cases of anaphylaxis and one anaphylactoid reaction in the HAE clinical program.

For the purposes of the agency's clinical review, all adverse events that were identified as anaphylaxis or anaphylactoid by the applicant were categorized as anaphylaxis.

In addition, the agency relied on the diagnostic criteria outlined by the 2006 Joint National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network's second symposium on anaphylaxis to identify potential additional cases from the safety database.

These are the criteria that the agency now uses in its assessment of anaphylaxis for other drug development programs, but please note that they were not published until after the EDEMA3 and EDEMA4 studies were conceived.

The specifics of these criteria are presented in this slide. I will not read through all of the points, but I would like to call your attention to three key factors.

First of all, I would like to emphasize that the criteria do not make a distinction based on the presumed underlying mechanism. Secondly, as you can see, HAE symptoms, like strata or abdominal pain, may overlap with anaphylaxis symptoms.

Certain signs and symptoms of anaphylaxis, such as urticaria, pruritis and bronchospasm, are not ordinarily associated with HAE and can be used to distinguish the two entities from one another. However, these distinguishing features are not always present in anaphylaxis, which means that some cases of anaphylaxis occurring in an HAE population may go undiagnosed.

Finally, please note that the cases of anaphylaxis that I'm about to present to you were identified using the most conservative criteria under number one. This particular subset of criteria does not assume that the drug is immunogenic, even though we know from the antibody data that ecallantide is immunogenic.

Using these diagnostic criteria, the agency's review identified four additional potential cases of anaphylaxis for a total of eight cases in the HAE program. Based on this, the estimated frequency of anaphylaxis is 3.7 percent of HAE patients or 1.3 percent of all

doses administered.

These rate calculations do not include patients who received ecallantide through compassionate use or patients from the cardiac surgery study.

The applicant did identify one additional potential case of anaphylaxis in a cardiac surgical patient. This patient had life-threatening hypotension and bronchoconstriction following receipt of ecallantide.

However, we have excluded these patients from the discussion for now since the perioperative conditions and surgical co-morbidities limit comparisons between them and the HAE population.

There were seven other cases that were suggestive of Type I hypersensitivity reactions in the HAE population, but these cases did not meet all of the diagnostic criteria for anaphylaxis.

For example, one patient developed flushing, urticaria, and pruritis within one

minute of completing her sixth intravenous infusion.

Another patient experienced allergic rhinitis-type symptoms, such as sneezing and congestion, within minutes of her first intravenous infusion and then again during a re-challenge procedure. There were also five other cases of isolated or generalized pruritis following injection with ecallantide.

To give a sense of the scope and severity of these reactions, I will now briefly describe four selected cases of anaphylaxis.

The first two cases are those identified by the applicant, while the latter two are additional example cases identified using the joint symposium's criteria. Full descriptions of all eight identified cases can be found in the briefing package.

Patient A from EDEMA3 experienced anaphylaxis twice, the first time after her 17th dose and the second time during a re-challenge procedure. Both events occurred within minutes of

dosing.

The first event was characterized by generalized erythema, pruritis, decreased blood pressure, and decreased oxygen saturation. She was emergently treated with epinephrine, diphenhydramine, and supplemental oxygen, and her blood pressure increased.

The second event was characterized by dyspnea, generalized rash, anxiety, pharyngeal edema, vomiting, diarrhea, urinary incontinence, hypotension and hypoxia following re-challenge with a one milligram subcutaneous dose.

This patient was noted to have tested intermittently positive to IgE against P. pastoris up to two years before the first event, as well as having non IgE antibodies to ecallantide.

Patient B developed anaphylaxis after her fourth dose of ecallantide in the EDEMA4 open-label study. Her symptoms consisted of acute erythema, generalized pruritis, tingling of the tongue, lethargy, change in mental state, and vomiting.

She was treated with two doses of epinephrine, hydroxyzine, steroids and IV fluids. A serum tryptase taken six hours after the event was elevated at 30 nanograms per milliliter, consistent with mediator release that would suggest an anaphylactic event.

The patient had intermittently tested positive for non-IgE and IgE antibodies to ecallantide since her second and third doses, respectively, but she did test negative to IgE ecallantide immediately prior to this event.

Patient C from EDEMA1 developed rhinitis, itchy throat and shortness of breath following her first dose of intravenous ecallantide. The patient was treated with epinephrine, antihistamines, corticosteroids.

This patient later underwent a re-challenge procedure and developed acute rhinitis symptoms after the start of the test dose infusion. This patient has not tested positive for antibody formation to the drug product.

Finally, patient D from EDEMA1

experienced sneezing, throat itchiness, congestion, rhinorrhea, shortness of breath and wheezing after the first intravenous dose of ecallantide.

The patient also experienced acute allergic rhinitis symptoms immediately following the second and fourth doses in EDEMA2. This patient later successfully passed a re-challenge two years later but has not had any subsequent doses.

In order to further define the hypersensitivity reactions observed with ecallantide, the applicant conducted a formal re-challenge study. Patients with a history of ecallantide hypersensitivity were invited to enroll.

The study consisted of two phases, the skin testing phase and a test dose phase using escalating doses of ecallantide. Nine patients total underwent the re-challenge testing procedures. Three patients had a positive re-challenge.

Patient 1, who is Patient A from the previous slide, experienced anaphylaxis during EDEMA3, had anaphylaxis again seven minutes after the one milligram subcutaneous test dose.

Patient 2 had originally experienced acute alert rhinitis symptoms, orbital swelling and urticaria after her first dose of ecallantide in EDEMA2. In the re-challenge study, 18 months later, she developed sneezing, rhinorrhea, cough, nasal congestion, and throat itchiness eight minutes after the test dose infusion.

This patient had tested positive for IgE antibodies to P. pastoris but subsequent assays have been negative.

Patient 3 originally experienced pruritis and nausea acutely after receiving a fourth dose of ecallantide. In the re-challenge study, she had a positive intradermal test at a one to 10,000 dilution and did not receive any further doses. This patient also has tested positive for IgE against P. pastoris.

Six of the nine patients successfully

completed the test dosing phase and four of the six have gone on to participate in other ecallantide studies without any other additional hypersensitivity reactions.

Although the sample size is limited to nine patients, the re-challenge study suggests that re-challenge may be a viable method for screening out patients at risk for future reactions.

However, we do not interpret the negative re-challenges to mean that the original reactions were not true hypersensitivity reactions. Negative re-challenges may be due to a loss of sensitization over time or the absence of certain co-factors that were present during the original reaction.

While the positive re-challenge rate of around 33 percent may seem low, this rate is actually higher than the range of positive re-challenge rates reported in the literature for some other drugs that are known to cause anaphylaxis.

As we can see from the anaphylaxis cases, several patients developed antibodies to both ecallantide and P. pastoris, the yeast medium that is used to produce ecallantide. However, these antibodies do not appear to be specific for hypersensitivity reactions, as a number of patients without clinical reactions also had evidence of seroconversion.

The figure shown here is a Kaplan-Meier analysis of the probability of seroconversion to IgE and non-IgE antibodies to ecallantide relative to the number of treated HAE attacks, which is shown along the X-axis.

The numbers shown along different points of the curve represent the number of patients who have been treated for at least that number of attacks. The probability of seroconversion increased with the number of treated episodes through five episodes and the estimated rate of seroconversion after eight attacks is approximately 30 percent.

There were few patients treated for more

than HAE attacks, so extrapolation beyond this point is not possible.

Based on the agency's review, the IgE and neutralizing antibody assays appear to be limited in sensitivity, so we may be underestimating the true rate of seroconversion. Also, HAE is a lifelong condition and patients may be expected to use ecallantide intermittently for many years.

It may be that patients continue to seroconvert with increasing exposure. The long-term consequences of seroconversion are not known at this time.

Aside from hypersensitivity reactions, there were no apparent differences in the overall frequency of adverse events reported in patients with and without antibodies to ecallantide. There were some differences noted for individual adverse events, but their disparate nature makes it difficult to draw any conclusions based on this limited population.

I would now like to conclude the agency's presentation with a summary of our main findings.

In terms of efficacy, the results of EDEMA3 were generally supportive, but the results were not statistically significant. As presented earlier, two patients mistakenly received the wrong dose and this error in two patients appears to have significantly impacted the findings.

EDEMA4 results, on the other hand, do show a statistically significant benefit for ecallantide over placebo. However, further analysis of the results pre and post sample size change have raised questions about the robustness of these results. Whether these results reflect the underlying variability of the disease remains uncertain.

In addition, while the clinical program intended to study patients down to the age of 10 years, a limited number of pediatric patients were treated with ecallantide. While ecallantide is not expected to be behave differently in younger patients, the extent to which adult safety and efficacy data can be extrapolated to the pediatric population is up for discussion.

In terms of safety, anaphylaxis is the major safety concern. Ecallantide is immunogenic and the long-term consequences of antibody formation are not known.

While several patients with hypersensitivity reactions appear to have antibody formation against the drug, the presence of antibodies was not predictive. Again, as is the case for efficacy, the amount of safety data in children is limited.

In summary, the agency recognizes the difficulty in conducting an adequate clinical program for a rare disease like HAE and remains committed to promoting the development of safe and efficacious therapies for such orphan diseases.

Whether ecallantide is an efficacious treatment for acute attacks of HAE is not entirely clear from the data submitted. Therefore, we ask the committee to consider the following questions.

Question 1. Discuss the hypersensitivity and anaphylaxis data and provide recommendations for further evaluation, if necessary.

Question 2. Does the data provide substantial and convincing evidence that ecallantide provides a clinically meaningful beneficial effect on acute attacks of hereditary angioedema in patients 18 years of age and older and in patients 10 to 17 years of age, and if not, what further efficacy data should be obtained?

Question 3. Has the safety of ecallantide been adequately assessed for the treatment of acute attacks of hereditary angioedema in patients 18 years of age and older and, again, in patients 10 to 17 years of age? If not, what further safety data should be obtained?

Question 4. Do the safety and efficacy data provide substantial and convincing evidence to support the approval of ecallantide for the treatment of acute attacks of hereditary angioedema? If not, what additional information is necessary to support approval?

Please note that unlike the previous two questions, this question is not divided into age subgroups. You will be asked to vote on this

question based on the applicant's proposed indication, which includes patients ages 10 years and older. You may comment after you vote and we will take these comments into consideration.

Finally, Question 5. Does the committee have recommendations regarding labeling, risk mitigation strategies for hypersensitivity and anaphylaxis reactions, potential for self-administration or other issues?

We appreciate the opportunity to present these issues to a larger forum today and look forward to hearing your discussion on these topics this afternoon.

Thank you.

DR. CALHOUN: Okay. Thank you to the FDA for their presentation.

So we've heard two very different views of the data and I think we'll have opportunity to discuss the implications of those quite discrepant views of the data later on. What I'd like to do is focus our attention in the next 15 minutes on specific clarifications of the FDA presentation

and not debate those two interpretations.

Again, taking chairman's prerogative once again, I have two, I think, simple clarification questions.

The first is how is it -- how did it happen that two patients in EDEMA3 were given the wrong drug, number one. And part B to that question is how was the error discovered.

DR. LIMB: I believe the company may be better suited to answer that question.

DR. HORN: If it's appropriate, I can take that.

DR. CALHOUN: Please.

DR. HORN: So the randomization for ecallantide used an interactive voice response system where the investigator called in, was given vial numbers for the drug to be administered to the patient, and then the vial numbers were entered into the CRF.

As a matter of chance, two patients showed up to the same investigator site at approximately the same time. The investigator

called in and got two vial assignments.

Those vial assignments were given to the patients and as the investigator staff, right at the time, was entering the numbers into the CRF, they realized that they had made a mistake. So that switch was noted immediately.

The investigator, the patient and the sponsor remained blinded until the unlock of the database at the end of the study. Those patients continued on following all protocol procedures and just continued with the study and data collection as planned.

DR. CALHOUN: The second technical question regards a biostatistical implication of the way the TOS was developed, and that is it was a dual binary as opposed to a five-point scale. I guess it was a ternary followed by two binaries.

That is, you were either worse, you were better or you were the same. And then if you were better or you were worse, it was much better or a little better or much worse or a lot worse.

If one were to ask that question with a

five-point scale, people tend to avoid the ends of the scale and one might think that by using that initial three-way split followed by a two-way split, one might expand the scale.

So I'd just like some clarification either from the industry or, Dr. Proschan, you might have some thoughts about that, about what the implications of the way that those data were generated have on the magnitude of the data.

DR. LIU: I think this depends on how the category for treatment outcome scores for each symptom. The company might have better comments on the separation of each scale.

DR. CALHOUN: Maybe I can simplify the question.

Why did you select a three-way split followed by a second two-way split as opposed to using a five-point scale?

DR. HORN: There were a couple of reasons for that. First of all, it was to avoid the simple thing that you mentioned. If you have a five-way split, people do tend to avoid the

endpoints and cluster toward the middle, and so we wanted to separate that out.

The other is in the design of a PRO, we wanted to make it as simple as possible. So we give people three choices initially, I feel better, I feel worse or I feel the same, and then divide it down by I feel worse, do I feel a lot worse or a little worse. So it was a combination of simplicity and the scales.

DR. CALHOUN: Okay. Dr. Schatz?

DR. SCHATZ: The concept mentioned before, the fact that the MSCS is weighted a little bit peripherally, because there are three versus the other two, and you've done a number of sensitivity analyses or reanalysis, I wonder if you looked at what the data would look like if it were only three areas that were included in the MSCS, that is, peripheral, combining all there of them together, but not weighted three times, laryngeal and abdominal.

DR. LIU: We didn't do that analysis based on three scales. So the data is not

available at the moment. But we'd like to make that analysis at the end of the review.

DR. CALHOUN: Mr. Proschan?

DR. PROSCHAN: In the briefing packet and in Dr. Liu's slide 2, there were two dotted lines and I just want to make sure I understand those. So I don't know if you want to put slide 2 up.

Maybe it's not that one. The one that had two dotted lines. Slide 4. Okay. That just has one.

Yes. So the 52, is that the number to the left of the rightmost line or the number to the left of the leftmost line?

DR. LIU: That's the number to the left of the line. So the number of patients to the left of the black dotted line are the predefined 52 patients and the dots in the right-hand side of the black dotted line are the additional 44 patients.

DR. PROSCHAN: Okay. I have to point out that I'm not very good at discerning the difference between those two colors. So is the

black one the right one?
DR. LIU: Yes, yes. Sorry.
DR. PROSCHAN: The right side. Okay.
So why do you have those two lines? I mean, why do you have -- after you changed the protocol -- but if those originally -- if you were planning to go to 52 anyway, why even look at that leftmost line, unless you think that somehow as soon as they changed the protocol, they started thinking differently or something?
DR. LIU: That's a good question. We actually had analysis results available for the separation based on the blue dotted line, but we didn't present it here. It's not substantially different from splitting the population based on the black dotted line, so the conclusion wouldn't change.
DR. CALHOUN: Dr. Gruchalla?
DR. GRUCHALLA: Yes. I believe, Dr. Limb, you were saying that the presence of IgE was not predictive. The question I have is was it -- so maybe seroconversion alone is not what's

important, also, but the quantity of IgE.
Were titers of IgE able to be analyzed in the study? That's the first question.
The second one is were IgE antibodies to the drug looked at before and then after drug treatment? Because the other question I have is, is there any kind of cross-reactivity between that agent and any other type of drug? So basically, those are the two questions.
DR. LIMB: Yes, IgE titers were taken. But based on those titers and the hypersensitivity reactions we identified, there wasn't any clear correlation, and the patient who appeared to have the most severe reaction, with anaphylaxis two times, her titers in particular were intermittently positive and negative.
And that may get back to the original issue we've had with looking at the assays, that there may be sensitivity issues.
I'm sorry. And then your second question?
DR. GRUCHALLA: The second question, was

IgE, drug-specific IgE, looked at before and then after the drug was given, because I don't know if there's -- could this drug be cross-reactive to something else, say, penicillin, which I know that's not the case. But could they have preexisting IgE antibodies?
DR. LIMB: So no IgE was detected at baseline against the drug product. I believe it was not until the fourth treatment episode that IgE was detected.
DR. ADKINSON: Dr. Limb, I didn't hear this in your presentation, but in the agency's briefing document, you raised a concern, which I share, that in theory, antibodies directed against the product might have an adverse perturbation of the intrinsic clotting system and lead to some state of hypercoagulability if they persist over time.
Has data been provide with regard to that potential possibility in any of these studies? Has the sponsor addressed this in any way?
DR. LIMB: I believe the company is in

the process of conducting in vitro cross-reactivity studies to look at that question. In terms of the clinical data, we didn't see any evidence of increased thrombotic events in the adverse events.
DR. ADKINSON: That would be a pretty crude, though, outcome.
DR. LIMB: That's true.
DR. ADKINSON: So no coagulation studies were done as part of these clinical trials, the pivotal clinical trials?
DR. LIMB: Coagulation parameters were studied serially, assessed serially, because we were actually concerned about a prolongation in the PTG based on animal -- I'm sorry -- in vitro studies.
And there was some slight prolongation of APTG that was seen, but it wasn't clinically significant. And then as far as the converse situation with hypercoagulability, we didn't see any events to suggest that was the case.
DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: Dr. Liu, could you please address my earlier question about the multiple statistical analysis, for example, in the comparison of the first -- in EDEMA4, in a comparison of the first 52 versus 44?

That data was analyzed at least twice, the first time, the whole group, and then the subgroups, and then you've repeated the analysis, and then there were the other analyses. And I'm just wondering whether there is an increased risk of a Type I error.

DR. LIU: These analyses are actually independent. So either you analyze the data based on the whole population or you analyze data based on the study period. So because they're independent, there is no correction on the Type I error.

DR. HENDELES: Maybe my biostatistics professor was wrong, but I was taught that if you keep on doing tests, that you have to make some kind of adjustment, because eventually -- I mean, you have at least a five percent chance of finding

a difference when no difference exists, and the more tests you do, the more likely you're going to find a difference.

DR. LIU: That is correct, but it's based on you do sequential tests. So this is actually based on independent look at the data in two different ways. It's not the same set of data tested by two different kind of hypotheses.

DR. PERMUTT: I think what Dr. Liu says is true about any given single analysis. I think your point is well taken that there are a lot of different things that we're looking at here and the probability for any one of them to go wrong is quite a bit more than the nominal probability of error in a single test.

In particular, the usual way of dealing with that in the FDA's work is to carefully pre-specify the primary analysis.

And it's worth noting that what you got from the sponsor is not the carefully pre-specified primary analysis of the individual studies, but a pooled analysis that was decided on

post hoc and it makes the overall data look rather better than the separate analyses of the individual studies.

DR. CALHOUN: Dr. Borish?

DR. BORISH: Yes. Could someone put up Dr. Limb's slide 22?

Part of the concerns raised about this -- Dr. Limb, slide 22 -- were the differences in the performance of the initial enrolled subjects versus after the sample size was increased. And when I look at the comparison in slide 22 of the difference in this group, there's a number that really jumps out at you that these patients are quite different.

The only objective data we have as to the severity of the patient's disease is their functional C1 inhibitor concentrations, and in the second half of the study, those numbers substantially drop.

Now, this being an autosomal -- now, the functional, of course, reflects -- so I'm referring to the line there where it says "mean

percent lower" -- lowest functional C1 inhibitor, left-hand side, 30.29, much, much lower on the right-hand side. So those are the only objective data we have as to these patients' disease.

As an autosomal dominant -- that number, first of all, is a function both of how much protein they have and whether that protein works or not. So it's an amalgam of both of those statistics. I don't know how much C1 inhibitor it takes to inhibit C1. I don't know how much it takes to inhibit kallikrein. But clearly, the later patients can't do either very well.

Now, I suspect when they went to the second half, I think we heard this, the company had to expand the number of sites, given the rarity of this disease and it's an orphan disease. And knowing the ways of the world, I suspect that when they expanded the number of sites, they did exactly what I would predict.

Sites who were, for lack of a better word, desperate or who had desperate patients who were doing extremely poorly were the ones that

were rushed to enroll in the study and rushed to enroll those specific patients in the study.

And I think it's the patients who have much worse disease objectively by these numbers who are clearly going to be the responders or, to put it another way, when you only have 13 percent functional C1 inhibitor, then when you're in the placebo group, you are going to get worse.

I don't think those six patients are outliers. I think those six patients did poorly because that's what you do when you have 13 percent C1 inhibitor, whereas when you have 30 percent C1 inhibitor, maybe you do okay or hold your own.

But I would love to see a data analysis looking at how people did based on what their functional C1 inhibitor levels were. But there's a big difference between the two halves of this and I think it's probably because worse patients from different worse sites came in later.

DR. HENDELES: But those placebo groups did better in that second half.

DR. BORISH: No, no. The six outliers were -- that the six patients got worse in that second half of the study, whereas in the first half of the study, the placebo patients held their own.

DR. CALHOUN: Dr. Foggs?

DR. FOGGS: Concerning systemic anaphylaxis, I notice that the serum tryptase level was checked, but it seems as though some of the patients had that particular test excluded.

Was there a specific reason for that lack of uniformity in terms of post-anaphylaxis assessment?

In addition, that's a corollary to the re-challenge phenomena, because the matured tryptase has greater sensitivity and what was reported in the data was the total serum tryptase.

The second question is, is there any reason that the mature tryptase was not utilized instead of the total serum tryptase to increase sensitivity with regards to likelihood of recognizing activation of tissue mass cells?

DR. LIMB: The collection of serum tryptase was not systematic. The data that I gave you are what data were available. So the patients that I didn't present a serum tryptase level for were because there was no serum tryptase level to report.

In terms of the -- I'm sorry. And then you had a second question.

DR. FOGGS: Well, that essentially answers the second question as well.

My concern was that there was lack of protocol for post-systemic anaphylaxis assessment with regards to a test that has significant utility in delineating whether or not the patients had systemic anaphylaxis, realizing that the patients who had normal serum tryptase levels could still have had systemic anaphylaxis, which is why I recommended the mature tryptase level. I think that should part of a protocol.

DR. LIMB: I will add that, at least in the patient who had severe anaphylaxis in EDEMA3, there was an attempt to obtain serum tryptase, but

they couldn't establish IV access. So I think individual investigators may have attempted to obtain that information, but it wasn't included in the protocol.

DR. CALHOUN: Dr. Hubbard?

DR. HUBBARD: Yes. I have a question. I think it's for the sponsor. But I've noticed something in the tables provided by the agency and that has to do with the schedule of procedures in EDEMA3 and in EDEMA4.

And I guess it leads me to question exactly how was the study done, because in EDEMA3, I see that the symptom complex assessment and the severity assessments were done by a phone call.

Does that mean the patients were ambulatory and had gone home? And then in EDEMA4, I see that it was done via e-diary.

So it looks like the assessments were done different ways for each study, so I don't know how comparable they are, because if you have patient-reported outcomes, they usually have to be done the same way. And I wondered whether the

patients were actually in clinic during all their evaluation or were they ambulatory?

DR. HORN: In both of the Phase 3 studies, the endpoints and the time points collected for the PRO were captured in the electronic diary and they were entered directly into the electronic diary at all time points.

The patients went to an investigator site. They were dosed with study medication. They remained in that investigator's site for the first four hours or to collection of the primary endpoint.

After that point, they were sent home and at 24 hours, the diary went off and rang a bell. They got a call from the site at 24 hours reminding them to do the electronic diary, and they completed the electronic diary.

When they came in for the seven-day follow-up period, they brought the electronic diary with them. All that data was then transferred to the database from the electronic diary. But all data related to PRO was captured

directly into the electronic diary.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: Certainly, in other drugs we -- in other drug allergies, we've not been able to identify IgG or IgE antibodies many times. It many times is not the drug; it's some metabolite of the drug. And so I think that this lack of correlation between the specific IgE and the IgG data doesn't necessarily mean that this is not an allergy reaction.

In addition, we certainly saw evidence of several anaphylaxis cases that looked like a very definite anaphylaxis. But I wonder how many other anaphylaxis cases we might have seen if these patients had not been treated.

So I presume and would ask did patients receive treatment, that is, patients that came in, they were treated. They were also getting standard treatment, which may not work, but it includes H1 and H2 antihistamines, includes epinephrine, includes steroids. These things may not stop angioedema, but they may stop

anaphylaxis.

DR. CALHOUN: Is there a response? That's an important point.

Dr. Ballow?

DR. BALLOW: I also want to follow-up on these hypersensitivity reactions. We've heard some information that the testing -- I guess it's RAST testing, IgE specific. It doesn't really correlate in many of these patients.

And then there was some reference, I think, in the documentation that there was also IgG antibodies, but we didn't hear very much data on that part of the in vitro testing.

We didn't hear anything about what the mode is or the molecule to which either the IgE or the IgG antibody specificity is directed against. We know it's made in yeast. And there was one comment that there were IgG antibodies in some yeast component.

So there's a lot of information that in order to try to figure out what the scope of these hypersensitivity reactions are, we don't have

enough information. Now, maybe that's one of the questions that the FDA is asking in their first question.

But is there any data, more data available about what part of the molecule it's directed? Is it directed against the yeast? Is it directed against the glycosylation point, as we've seen with some of the monoclonal antibodies at Dr. Borish's institute, with cetuximab? We need more information to try to understand more about these hypersensitivity reactions.

DR. LIMB: I think you've raised several good points and, certainly, I think our first question goes into some of that.

As far as the IgE antibodies go, I don't have additional information aside from what's already been provided in the briefing package regarding what specific moiety might be involved, and I think a lot of that still has to be worked out.

So really what we're basing our safety assessment on is on what we've seen clinically,

and that is that there are cases of anaphylaxis and that it occurs at a rate greater than two percent, maybe somewhere as high as four percent or even higher, if there are cases that are going undiagnosed.

DR. CALHOUN: Finally, for this morning, Dr. Hoidal.

DR. HOIDAL: Just a couple questions for Dr. Liu.

In the responder analysis that you presented, was that in the intention to treat as treated or in the intention to treat as randomized?

DR. LIU: As treated, intention as treated.

DR. HOIDAL: Okay. And then if one looks as these two indices, the TOS and the MSCS, do they distinguish themselves in any way in the robustness of response?

DR. LIU: I think the sponsor did some analysis about the correlation between the two efficacy endpoints, the correlation between TOS

and MSCS. Probably they have slides to show that.

Is that your question?

So this is based on the BLA submission. The sponsor did analysis on correlation between TOS and MSCS and there are not great correlations between the two efficacy endpoints. We don't have a slide to show that. That's the conclusion.

DR. CALHOUN: Okay. Thank you.

Again, for the sake of time, we're going to end discussion this morning. We will take a 52-minute lunch break. We're going to reconvene at 1:00 p.m. promptly. There will be time -- I know Dr. Adkinson has a question. There will be time following the lunch break and the open public hearing portion of the meeting for brisk and detailed discussion.

So thank you very much.

(Whereupon, at 12:05 p.m., a lunch recess was taken.)

AFTERNOON SESSION

DR. CALHOUN: Good afternoon, folks. The next item on the agenda this afternoon is the open public hearing.

The open public hearing, we have six speakers from the public. I'll announce them individually. They will have four minutes for their presentation. If there are questions specifically related to that presentation from the committee, we can take those at that time. We'll have the time to do that.

So this is the statement for the beginning of the open public hearing.

Both the Food and Drug Administration and the public believe it is a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing section of the advisory committee, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning

of your written or oral statement, to advise the committee of any financial relationships that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One

of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for your consideration.

So, again, before we start, five of our presenters are from the United States Hereditary Angioedema Association and they will be representing themselves.

The first of our speakers is Sally Urbaniak.

MS. URBANIAK: Good afternoon. My name is Sally Urbaniak. I live in Jacksonville, Florida. I very much appreciate having the opportunity to address the committee and the FDA staff.

The HAE Association paid for my travel here today and I have no financial ties to Dyax, other than a small number of shares that I have purchased as a symbolic gesture of my vigorous support for HAE research.

I want to take a slightly different approach during my time with you this afternoon. Let me start by asking each of you to step out of your roles as medical professionals and, for the next couple of minutes, think of me as your sister or your daughter. Please spend a few moments with me living the life of a severely affected HAE patient.

Imagine waking up one morning and as you get out of bed, you realize your feet are so swollen that even a short walk to the shower is going to be painful.

When you stand up, your feet feel like they are ready to explode from supporting your body weight. But soon you have no choice rather than to get moving, because a sharp, gnawing pain in your stomach signals a sickening and urgent need to throw up.

The fluids which cause the swelling have leaked out of your circulatory system and your blood pressure is very low. The lightheaded, faint feeling that you're experiencing, it makes

you wonder if you will even make it to the bathroom before passing out.

You want to ignore the dangers of not seeking medical help for what you know is going to be a miserable attack. You want to just stay home and tough it out. But then the next wave of excruciating pain hits and your spouse intervenes and convinces you to make another trip to the ER for fluids and pain medicine.

You are so weak. You can barely muster the strength to call in sick at work, but you have to. And when you do, you can sense your boss' frustration by the tone of his voice, because this is the second time you've called out sick in the past week and a half.

On your way to the hospital, you start thinking of how you're going to handle the ER staff's not so subtle questions that all but directly accuse you of being a drug seeker. You feel so weak and sick at this point, but you know those endless questions are coming.

Before you even arrive at the hospital,

your swallowing becomes more difficult and it feels like your throat is swelling. You're somewhat content that the car is just dark enough so your spouse doesn't notice how frightened you are that your throat is closing.

When you arrive at the ER, you say a silent prayer that you will not have to spend the next 72 hours looking at the glistening reflection of the surgical knives that the doctors have placed near your bed so they can swiftly cut a hole into your windpipe to prevent suffocation from a compromised airway.

Ladies and gentlemen, the pain, fear and emotion or emotional burden borne by me and thousands of other HAE patients is inordinately tragic because it's preventable. Clinical data shows that ecallantide is an effective (inaudible).

DR. CALHOUN: Thank you. Our next speaker is Jenny Barnes.

MS. BARNES: Good afternoon. My name is Jenny Barnes. I do not have any financial ties to

Dyax. I am not a shareholder. And the HAE Association paid for my travel here today.

I am appearing before you today, ladies and gentlemen, not as a patient, but as the mother of a severely affected young man with HAE.

My son, Jim, began suffering from severe abdominal attacks at the age of five. I can vividly recall the horror of having watched him suffer until the only medicine we could find at our disposal was Demerol that would mercifully put him to sleep.

In his subsequent years, Jim bravely endured frequent disabling swelling and pain. The relentless onslaught of HAE attacks resulted in an inordinate number of missed school days and prevented him from the day-to-day activities enjoyed by boys his age.

As if the pain -- I'm sorry. As if the pain and disability haunting Jim wasn't enough, he had his first laryngeal swelling attack at age 12. This dangerous life-threatening event required intubation in ICU that lasted three days.

The episode of laryngeal swelling provided tangible evidence that Jim's HAE was worsening, and at that point, we had no choice other than start him on an anabolic steroid.

While these medicines are contraindicated in 12-year-old boys, we concluded that the risk of death from asphyxiation outweighed those associated with androgen therapy in a prepubescent youngster.

The years of emotional trauma wrought by pain, the looming threat of death by suffocation, and anabolic steroid therapy took its toll on Jim. When he was 15, Jim suffered an emotional meltdown that was clearly steroid-related. The steroid rage that Jim exhibited landed him in protective custody setting.

In the past two years, Jim began to show a glimmer of promise, thanks to intensive therapy and the fact that his growth into a man diminished some of the steroid effects. By age 19, he had a job and we finally began to see the makings of a young man that was proving himself to be an asset

to society.

I won't know what kind of man Jim was going to become, because on June the 6th, 2008, he had a laryngeal attack and he went to the emergency room where he later died. The autopsy labeled asphyxiation due to laryngeal edema.

I am here addressing you today because Jim's death and the passing of at least three other patients who suffocated from acute HAE attacks over the past 18 months were totally preventable.

Ecallantide, the product before you today, has been shown to be an effective therapy for stopping throat swelling swiftly. Clearly, if available, this medicine would have saved my precious son's life.

I stand before you heartbroken, but resolute in desire to do whatever I can to prevent another mother from the unspeakable grief that accompanies losing a child to HAE.

I will never have the privilege of celebrating my son's achievements, helping him

through life's inevitable bumps, or experiencing the joys of attending his wedding, holding my grandchildren, celebrating his successes, and share in his life's milestones.

You have the power today to approve ecallantide and, in doing so, ensure that no other HAE mother ever shares a story like mine. He did not have to die, suffocating this way, and he suffocated and it's not acceptable.

I respect you and I thank you for your time.

DR. CALHOUN: Thank you.

The next speaker is Dr. Henry Li.

DR. LI: Good afternoon. A financial disclosure, I was a PI and a consultant for Dyax as well as the four other companies who are involved in the HAE treatment development.

HAE Association invited me to speak here on behalf of the community of physicians as well as HAE patients, but nobody pays me to be here. I do not own any stock in any of the companies.

I'm a practicing allergist and I also

hold academic appointment in Georgetown University Medical Center as well as the Johns Hopkins Asthma-Allergy Center.

I am here today to provide the committee and the FDA staff the viewpoint of a physician who is taking care of more than 50 HAE patients. Most of my patients participated in various HAE clinical trials. Many of them involved and benefitted tremendously from the treatment using ecallantide for their acute HAE attacks.

I personally witness how access to end prudent use of this remarkable medicine aborted and controlled their otherwise disabling severe attacks. This medicine provided perhaps the most dramatic improvement in many of my patients suffering from their HAE attacks.

At this time, however, there are no approved medicines for HAE patients for their acute attacks. Despite the recent approval of the C1 esterase inhibitor for prophylaxis, many of my patients are not able to meet the criteria to receive regular C1 esterase infusion for

prophylaxis.

Even for patients who are on C1 esterase inhibitor for prophylaxis, many of them may still have occasion to have breakthrough attacks.

There is an urgent need for such a medicine which can quickly relieve and abort HAE attacks. Without such a medicine, many of my patients are living in the constant threat and fear of another potentially life-threatening HAE attack, which may result in a few days, even a week of agony.

Many attacks require emergency room visits and even hospitalization, intubation and intensive care stay, not only costly, but also emotionally and physically draining.

The HAE patient community would be better served by the approval of an urgently needed and potentially life-saving medicine for their acute attacks, such as ecallantide.

Thank you.

DR. CALHOUN: Thank you.

Next on our list is Janet Long.

MS. JANET LONG: Good afternoon. My name is Janet Long and I am Vice President of the United States Hereditary Angioedema Association. I thank you for providing HAE patients with an opportunity to discuss the critical need for a safe and effective non-steroidal HAE therapy.

I do not have financial ties to Dyax. I am not a shareholder, and the HAE Association paid for my travel here today.

This afternoon, I'll be wearing two hats. I will begin by providing a perspective from my vantage point as an officer of the U.S. Hereditary Angioedema Association, the organization that represents well over 6,000 HAE patients in this country.

Because I am also a patient and have a story that represents what is experienced by people afflicted with HAE, I will following recount the suffering, fear and frustration that accompanies an arduous journey in search of HAE diagnosis and treatment.

Perhaps the best characterization of how

HAE affects patients appeared in a 1996 New England Journal of Medicine article.

I quote, "Patients with a deficiency of C1 inhibitor are not just an interesting model for study, they are critically ill and many have ancestors who died suddenly from suffocation. Patients live in constant dread of life-threatening laryngeal obstruction," end quote.

Ladies and gentlemen, three young, vibrant members of our HAE community have succumbed to that very life-threatening laryngeal swelling just this past year. The absence of an approved acute attack therapy for hereditary angioedema leaves an unmet medical need in its wake.

While 17 alpha alkylated anabolic steroids are useful for HAE prophylaxis in certain adults, the scientific literature reveals that many patients continue to experience periodic acute abdominal and laryngeal attacks, notwithstanding ongoing therapy.

Moreover, the utility of these potent male hormone derivatives is limited because they are not well tolerated by women, are directly linked to increased serum lipid levels and their use is contraindicated for children, many of whom, tragically, are severely affected and suffer frequent attacks.

We're delighted the committee will be considering ecallantide today. The clinical evidence shows that it is an effective medicine that will serve to save lives and ameliorate dreadful morbidity associated with excruciating abdominal and life-threatening laryngeal attacks.

Now I'll quickly put on my patient hat and discuss my personal experience.

The story of my lifelong struggle with HAE begins at age seven, with severe abdominal attacks and to this day, I am haunted by the face of my mother, who was only able to offer me a hot water bottle to put on my stomach and a few baby aspirin, which she knew would do nothing to ease my suffering.

At age 21, I experienced an abdominal episode that was so severe it caused internal bleeding, which led to an unnecessary exploratory laparotomy and days in the intensive care unit.

Laryngeal attacks came next, completely closing my airway. I saw scores of doctors who either admitted to being totally baffled or offered diagnostic theories that never hit the mark.

I tired of showing up to the emergency room only to be sent home after being told that nothing could be done and I would have to learn to live with my condition.

I remember vividly one night, a very devastating abdominal attack and curled up in agony. I told my husband, "I don't know if I will make it through the night. Please tell my three beautiful girls that I love them."

Finally, after almost 40 years of horrific suffering, with the prospect of living getting bleaker and the attacks continuing unabated, a gastroenterologist to whom I was

referred persevered until she got to the bottom of my illness and came up with a diagnosis of hereditary angioedema. I was prescribed androgens and, like every female patient, I endure their embarrassing and horrible side effects.

Today, you have before you an abundance of clinical (inaudible).

DR. CALHOUN: Okay. Thank you.

Next is Michelle Williamson.

MS. WILLIAMSON: Good afternoon. My name is Michelle Williamson. I do not have any financial ties to Dyax. I'm not a shareholder, and the HAE Association paid for my travel here today.

I'm one of the hundreds, if not thousands of HAE patients for whom 17 alpha alkylated androgens are not effective. In addition, I'm a living, breathing example of why HAE patients in the United States desperately need an acute attack therapy.

During 23 long years of androgen therapy, I've suffered through countless emergency room

visits, many of which involved compromised airway, resulted in more than a dozen intubations, and one emergency tracheotomy.

The tragedy that almost took my life this last February illustrates why the HAE patient community -- keep in mind patients who obtain relief from androgens are still prone to breakthrough attacks -- need access to an acute therapy.

I took a brief vacation to the Rocky Mountains just for the weekend. I had what can only be described as an idyllic getaway. That was until HAE cruelly asserted itself.

While driving to the airport to catch a return flight home, I realized I was experiencing a laryngeal attack and it was coming on fast. My boyfriend noticed that my voice pitch had changed. I was beginning to have difficulty breathing and swallowing, so we flagged down a police officer who was able to call an ambulance.

At the emergency room, despite my objections, the doctors treated me with medicines

HAE patients know do not work, epinephrine and Benadryl. They also tried fresh-frozen plasma, to no avail.

The advance of the swelling attack and the baffled look on the faces of the ER physicians made me fear for my life. I prepared myself to die, again. I told my boyfriend to tell my son that I loved him -- he also has HAE -- and that I was sorry; for him to call my mom, call my sisters.

As I lay helpless with my airway tightening, I remember coughing and then nothing else. I spent the next seven days intubated and sedated. My lungs had collapsed. I lost the use of my leg muscles from being bedridden. I could barely manage to sit up until day 11. I managed to take three steps that day and I hyperventilated and I fainted.

I woke up hearing the doctors trying to decide whether or not to intubate again and telling me I should consider a permanent tracheotomy. After 19 days in the hospital and an

$80,000 bill, I was sent home with antibiotics to treat hospital acquired pneumonia and I endured weeks of rebuilding leg muscles so I could walk again.

The tragedy is this traumatic and costly situation could have been completely avoided if an acute attack therapy, like ecallantide, had been available.

So as you deliberate approving the Dyax product today, I kindly ask you to consider HAE patients like me who so desperately need this life-saving therapy.

Thank you.

DR. CALHOUN: Thank you.

Our last presentation is by Jenna Long.

MS. JENNA LONG: Hello. My name is Jenna Long. I do not have any financial ties to Dyax and the HAE Association paid for my travel to come here today.

As we all know, HAE is a genetic condition that runs in families. And I am the 16-year-old daughter of Janet Long. I am here to

provide a teenager's point of view of what it is like to have HAE and to discuss my experiences with ecallantide, the medicine that you are evaluating today.

I had my first HAE attack when I was nine years old. I remember walking into the kitchen, where my entire family was gathered, and being greeted by sudden silence and concerned looks. It was obvious to my parents that my face was swelling and the next thing I knew, my mom was on the phone to the hospital talking to an allergy specialist who treats HAE.

Despite my mom's best efforts to calmly describe HAE to me when I was nine years old, I recall being scared and also wondering how this disease would affect me as I grew up.

It was frightening to know that my mom had to know right away if I had a funny feeling in my throat or I was having trouble swallowing or breathing. It was very scary to know that an HAE throat attack was dangerous, because it made me worry if there would be enough time to get to the

hospital before the swelling would stop me from breathing.

My mom recognized the fear and uncertainty brought by HAE was affecting me a lot. So she did some research and found out about trial medications and then enrolled me in an ecallantide clinical trial.

Ladies and gentlemen, it was great to know that my mom could take me to the hospital, where I could be given medicine to stop a horrible stomach attack or to make sure that my throat would not swell to the point where I could no longer breathe. Having ecallantide alleviated my fear.

I have had several throat attacks since being enrolled in the ecallantide trial, including one in which my tongue swelled so big I couldn't talk. On each occasion that I received ecallantide, I felt better within a half an hour. I was also amazed at how fast the medicine reduced the swelling I was experiencing.

I am very grateful to have a medicine

that can actually help me, although I do still feel bad knowing that my mom had to suffer all those years without any treatment at all. Knowing that a medicine like ecallantide will be available makes me feel hope and lifts my spirits, because now living a normal life, just like my friends, is possible.

Having an effective therapy for attacks means I can participate in school activities without fear that an attack might threaten my life. Also, I can consider going away to college, something that would not have been possible without a medicine like ecallantide.

Having ecallantide available to treat HAE attacks has changed my life. Knowing that this medicine is available has greatly eased my fear of pain and death. There are thousands of HAE patients, including young people just like me, who also deserve to live a normal life. I ask you to consider us while discussing the approval of ecallantide.

I thank you.

DR. CALHOUN: Okay. Thank you.

On behalf of the committee, let me thank each of the patient representatives for reminding us of how profoundly this disease can affect your lives. Thank you.

Are there questions for any of the public hearing speakers from the committee? Dr. Terry?

DR. TERRY: I think it was Ms. Long who was a representative of the foundation. I wanted to ask, has the Dyax Corporation contributed financially in any way to the HAE Foundation, whether it's in terms of financial aid in recruiting patients or in any other form?

MS. JANET LONG: No. There has been none of that. I believe there has been an educational grant that is normally collected by the HAE Association at our conferences whenever pharmaceutical companies come. We welcome them all as a product-neutral organization, and they normally fund us with an educational grant for that conference for our patients.

DR. CALHOUN: Are there other questions

for the public hearing representatives? Okay.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, which is the careful consideration of the data before the committee, as well as the public comments.

So at this point, we'll begin the panel discussion portion of the meeting. It's open to public observers, but, again, public attendees may not participate, except at the specific request of the panel.

So there are some residual questions perhaps left over from the sponsor presentation. There are some residual questions left over from the FDA presentation. And there may be some issues that have come up with respect to the open public hearing presentations. So let's take care of those first and after that, then we'll move on to discuss questions.

Dr. Honsinger?

DR. HONSINGER: I have three questions, one for the FDA.

This drug is being approved for orphan drug status. Educate us a bit about orphan drug status.

Will approval of this drug hamper approval of any other drugs that will be used to treat this orphan disease? That is, we know that there are kallikrein receptor inhibitors in the works as well, and will drugs like that still be able to come afore as an orphan drug?

The second question I have is about off-label use. This drug could well be useful for other diseases. We certainly see some patients who have angioedema that's life-threatening that don't have the C1 inhibitor deficiency, and a few of those have been reported in Europe.

We see patients who have a kallikrein-related disease when they have angioedema after using angiotensin converting enzyme inhibitors, the blood pressure drugs.

The third question is why was it chosen

to give three doses at three sites rather than a single dose to these patients?

DR. CHOWDHURY: I will take the questions 1 and 2 and then ask my colleagues to respond to Question 3.

As far as the Question 1, which is for orphan drug status, the orphan status is determined based on the number of patients that are there with the disease in the country.

So these are for rare diseases with a certain number of patients, which is small. As far as other drugs coming to the market for an orphan indication, the answer to that question is other drugs can come to the market, even if they target the same pathway or different pathways.

The point that comes with the orphan indication, as far as other drugs coming to the market, has to do with exclusivity. If a drug is approved for which clinical studies are required, which is true for any new drugs, then for that, the companies would get exclusivity.

For an orphan indication, the duration of

exclusivity is longer, longer by about two years compared to a normal orphan drug.

What that does is a generic cannot come for that duration. So that is all the orphan indication would do as far as other drugs coming to the market. A generic drug, which is the same drug, a duplicate copy, will not be coming to the market for two or three years. Other drugs can come.

The second question is off-label use. Off-label use is recognized and like this drug, if it is to be approved, or for other drugs, off-label use can happen.

We understand that, we acknowledge that, and that really has no direct implication on the safety and efficacy for this drug for the indication that we are discussing here. If you have any specific concerns about off-label use, we certainly would like to hear that and understand what the concerns are.

So the third question, I'll turn it over to the team.

DR. LIMB: I believe it was delivered as three separate injections because the solution comes as a 10 milligram per milliliter solution, and injections greater than one milliliter in size would be more painful to the patients. So I think it was a patient comfort issue. I don't know if the company has anything else they'd like to add.

DR. PULLMAN: No, that's exactly how we approached it in terms of the known tolerance of subcutaneous injections to keep it below 1.7 mils. So it was pragmatic to give it as three separate injections.

DR. CALHOUN: Dr. Schatz?

DR. SCHATZ: Two questions. I think I'll ask them one at a time.

The first is Larry Borish came up with, to me, a very astute observation and a hypothesis that there was a relationship between efficacy and baseline severity that seems to be testable in the entire dataset.

I wondered whether that, in fact, was tested either by the company or the FDA; that is,

a relationship between worst C1 esterase -- or between baseline C1 esterase percent functionality and eventual efficacy.

DR. LIU: We have backup slides to show that.

DR. SCHATZ: I'm sorry?

DR. LIU: We have backup slides to show that.

Can we go to 21?

So this plot is for change of MSCS versus baseline MSCS. The X-axis is baseline MSCS. The Y-axis is change of MSCS. So the Y-axis is the primary efficacy endpoint we're interested in.

The legend is not that big, but the R-square measures the correlation between the primary efficacy endpoint and the baseline. So R-square of one indicates perfect correlation, perfect linear correlation, and R-square close to zero indicates random distribution of Y on X. And from the results, this shows the correlation between Y and X is almost random.

Does that answer the question?

DR. CALHOUN: No. That's not the question, I don't believe.
DR. LIU: Oh, sorry.
DR. SCHATZ: No. The question was the relationship of efficacy to baseline C1 esterase inhibitor level.
DR. LIU: Oh, sorry, I got that question wrong. We don't have slides to show that. We didn't do analysis for the C1 inhibitor.
DR. SCHATZ: And I gather the company doesn't have those data either.
DR. HORN: No. Baseline C1 severity doesn't predict the severity -- baseline C1 level doesn't predict the severity of individual attacks. So what we do have is the efficacy based on the severity of attack for the single attack, but not by C1 levels in the patient.
DR. SCHATZ: Right. But I'm not so sure that that excludes the hypothesis that baseline C1 esterase level would predict responsiveness.
DR. HORN: Right.
DR. SCHATZ: And that hasn't been tested;

is that correct?
DR. HORN: No.
DR. SCHATZ: My second question -- I'm sorry.
DR. LIMB: I was just going to add that I think Dr. Borish and you have raised a good point and that's something that the agency is interested in looking at specifically, is the C1 inhibitor level and how it correlated to responses.
I think we were coming at it from an approach where we didn't think that it predicted individual severity at baseline, but certainly it could affect response to treatment.
DR. SCHATZ: And then my second question is, clearly, the most potentially severe are the laryngeal effects.
Has an analysis been done -- if the indication was made just for laryngeal attacks, would your efficacy data -- have you done the analysis and, if not, I would suggest perhaps it could be done, to see whether, with that specific site, whether the efficacy could look more robust.

DR. LIU: There is subgroup analysis on attack location and I think one of the sponsor's slides showed that, and we can go back to that slide again.
DR. SCHATZ: And I know that it showed that it looked like different sites made a difference, but I'm not totally sure that that's the same as using the entire data, or maybe it is, using the entire dataset to look at everybody who had laryngeal aspects of their symptom, but only look at the -- I think that slide might have been total MC, whatever it is, total symptom scores in those patients.
But maybe you could clarify what that is, what that was, and see if there we need more.
DR. HORN: So you're right. That is patients with a laryngeal attack, their composite MSCS. We have done the analysis of MSCS looking by attack location and severity and we can show you that information for the laryngeal attacks.
Slide up, please.
So then in this slide, we see the change

in MSCS score at four hours by laryngeal attack location, by severity, and this is in the integrated Phase 3 numbers.
And in here, again, the numbers are small, but we see for moderate attacks, the ecallantide group has a median of minus one and the placebo group has a median of minus .5, and, in severe attacks, ecallantide still has an MSCS change of minus one and placebo is minus 0.7.
DR. CALHOUN: Dr. Gruchalla?
DR. GRUCHALLA: I have a question, but I'm not sure it can be answered.
The patients had to present within eight hours of an attack; is that correct? Okay.
Did we see any greater effectiveness if it was given early on? But, again, I don't know if there's enough data. I mean, again, can --
We did see that? Oh, we did see that, and it did. Okay.
DR. CALHOUN: Dr. Proschan?
DR. PROSCHAN: I wanted to get back to the imputation for a second.

I guess how I interpret the imputation depends, in part, on whether it's reasonable that this drug could actually prevent -- not just treat the existing problems, but prevent future ones, at least short term. And I'm wondering if there's any data to that end.

So if you believe that this drug can actually prevent occurrences, then imputing for those people who get emergent symptoms seems like it does the right thing; that is, it assesses whether the drug helps at preventing. But I don't know if there was already some reason to believe that it might not just treat, but prevent.

DR. HORN: Slide up, please.

So this was the slide from the core presentation which looked at emerging symptoms after study drug administration, and the top three are patients who had emerging symptoms following ecallantide and the bottom are the patients who had emerging symptoms following placebo.

So there are fewer people with emerging symptoms following ecallantide administration than

following placebo administration.

Now, the other thing to consider is that the imputations that we're talking about for the primary analysis, including only emerging symptoms within the first four hours of treatment and only medical interventions within the first four hours of treatment, and the numbers there are very small.

For example, in EDEMA4, for emerging symptoms, there were two patients in the ecallantide group and four patients in the placebo group. In EDEMA3, there were zero patients in the ecallantide group and two patients in the placebo group with emerging symptoms.

A few more for medical interventions. For EDEMA4, there was one medical intervention in the ecallantide group and nine in the placebo group. And for EDEMA3, there were three in the ecallantide group and five in the placebo group. So the numbers with imputation for the primary endpoints are very small.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: Three questions. The first one is why wasn't a crossover design used since this is a drug with a two-hour half-life and, presumably, patients' episodes are separated by at least a week or more?

And the second question is did anybody calculate the number needed to treat to prevent one intubation or some morbidity marker like that? And third, is there any pharmacogenomic data in these patients as to who responds or doesn't respond?

DR. PULLMAN: We chose a standard parallel group approach as being the most efficient way to provide evidence of effectiveness over time, given the unpredictable nature of the attacks and the need to provide intervention on a randomized basis.

So that was our decision based on pragmatic considerations. But I take your point, and crossover designs could have been considered, but we decided not to approach it that way.

DR. HENDELES: Given the small number of

patients available, it would have certainly increased the power of your analysis.

My recommendation is if you do any future -- any additional studies, that you consider that study design.

DR. PULLMAN: Okay. Thank you.

With respect to calculating the rate to minimize laryngeal attacks, no, we have not done that. And pharmacogenomics, likewise, we don't have any information on that. There are about 150 discreet mutations affecting the gene and the C1 esterase, but it is an interesting question.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: I just wanted a little bit of clarification on a couple of things. We've learned from EDEMA2, I believe, that the dose information that we got from that study is what we have used with 30 milligrams subcue for the subsequent studies, including pediatric patients.

Is that correct?

DR. PULLMAN: Yes, that's correct.

We have that supported by population PK

analysis, in addition to EDEMA2. So the overall dataset from an efficacy perspective is EDEMA2 supported by population PK from EDEMA0, 1, 2 and the healthy subject studies.

DR. CARVALHO: So once we've established that dose, I am wondering if there's any kind of weight-based or body surface area-based types of data that we can get, for instance, for the incidence of anaphylaxis, since we've learned that immunoconversion and anaphylaxis do not necessarily correlate.

Is there any information from the size of the person and the dose that they're getting for immunoconversion, anaphylaxis, and effect?

DR. PULLMAN: On effect, we've looked at cuts by weight and I can review that data. On immunogenicity seroconversion, no, we don't appear to have any profile data.

And on the overall effect of weight on exposure, within that age cohort that we've studied, the 10 through 78, we did not see weight as a covariant affecting clearance and, therefore,

clearance would not affect exposure.

At the heavier body weights, it may slow up and increase lag time for the initial absorption phase. I can speak to -- well, I'll let Dr. Horn actually speak to the efficacy date we've looked at by body mass index above and below 30, as well as weigh above and below 200 pounds. But if you'd like to see that, we can pull that data up.

DR. HORN: Okay. So slide up, please.

So we evaluated weight with two parameters in mind. One was to look at the question of obesity and one was to try to drill down into some of the pediatric data.

So our first proposed cut was to look at weights from less than 100, 100 to 200, and greater than 200. But when we did that, when we ran our data, we found that even though we had the 25 pediatric patients, we only had two of those who weighed less than 100.

So that analysis wasn't run. It was just run as the less than 200 and greater than 200.

That calculation or that analysis is done if you look in the bottom part.

And there you see for weight less than 200 pounds, there were 47 patients treated with ecallantide, 45 patients treated with placebo. The median change for the ecallantide group was minus 1.0; for the placebo group, it was minus 0.3, and a highly significant P value.

For weight greater than 200, where the numbers were smaller, we see the same treatment effect, minus one and minus 0.2, but, again, because of the smaller numbers, the statistical significance is not there.

We have also analyzed adverse events by weight and apparently we don't have a slide on that right now. But again, in the overall adverse event profile, we don't find any changes between the under 200 and the over 200 nor do we see any -- like Dr. Pullman said, we don't see an increase in hypersensitivity or anaphylaxis or even seroconversion when we look at it that way.

DR. CALHOUN: Dr. Hubbard?

DR. HUBBARD: Yes. For the sponsor, while you're still here, I have a couple of questions.

First of all, was there any additional safety data from the compassionate use patients that you've given it to that might be of interest to us?

DR. HORN: We've had a total of eight patients receive compassionate use. Their safety profile is similar to overall.

DR. HUBBARD: Okay. A second question is do you have any data on reduction in steroid use in patients who have received ecallantide versus placebo?

DR. HORN: No, and we haven't looked at that, and that is because the studies were measured for acute attacks. So in the attacks, the patient could be on whatever their baseline was.

So some patients were on androgens and some patients were not on androgens. And even those that are followed in the open-label study,

we haven't followed whether or not they were switched off androgens or started on androgens.

DR. HUBBARD: Okay. And then, lastly, have you done any pharmacoeconomic modeling of what the impact of this may be?

DR. HORN: Not that I'm aware of. I mean, we do have a significant burden of illness study that we conducted with the HAE Association, which shows a very high financial burden and psychosocial burden to patients with HAE, but as yet, we don't have any evidence of how this will be affected by ecallantide treatment.

DR. CALHOUN: Dr. Hoidal?

DR. HOIDAL: I just want to push that idea of trying to identify objective indicators of response. And so the question is do you have any information on genotypic variability in relation to response or any indication of any environmental factors, age, anything that might interact with genotypic variability in terms of response?

DR. HORN: So we have not found any. We've looked at age in the pediatric population,

the adult population, the geriatric population. On both extremes, the numbers are very small, but treatment effects and safety profiles seem to be the same.

We've looked at weight, we've looked at gender, we've looked at the antibody status, we've looked at prior exposure to ecallantide, and in all those subgroup analyses, we see a consistent similar effect.

It's not too surprising in terms of genomics and pharmacokinetics, is this is a protein, so there is really no CYP enzyme involvement.

So you wouldn't expect any of those kind of genetic variabilities or genomic variabilities to make a difference in that. So we haven't identified any group of patients that either have a better response to ecallantide or do not respond to ecallantide.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: Two questions. The first one, is there any relationship between the serum

concentration and response? And the second question I have for Dr. Limb is how is the C1 inhibitor used and how effective is that at preventing laryngeal attacks?

DR. PULLMAN: I'm sorry. Your first question was on pharmacokinetic/pharmacodynamic relationships with respect to response?

DR. HENDELES: Actually, serum concentration of the drug in relationship to response.

DR. PULLMAN: Okay. And we have not seen one. We haven't conducted an extensive pharmacokinetic analysis with respect to outcome measures in the EDEMA3 and EDEMA4 trials. We did not collect pharmacokinetic samples.

And so early attempts at pharmacokinetic/pharmacodynamic relationships were based, in the initial EDEMA0 and EDEMA1 trial, on markers like plasma kallikrein and I think it was C2 levels. But we have not looked at the relationship between drug exposure and effect, except in EDEMA2. So that's the basis of the dose

selection.

DR. HENDELES: Given a 30 milligram dose, what's the range of concentrations, P concentrations that you would get in adults?

DR. PULLMAN: In and across the age range that we've studied, the coefficient of variation is approximately 25 percent. The Cmax concentration is approximately 600 micrograms per mil or 80 nanomolar, and the area under the curve is approximately 3,000, again, with the same coefficients of variation.

DR. HENDELES: But in that Cmax, what's the variation between -- what's the range of concentrations? Is it four-fold, eight-fold, two-fold?

DR. PULLMAN: I would have to get back to you on that one, but I think it's much less than that. It's relatively tight. I might be able to come back to you later in the session on that.

DR. CALHOUN: Dr. Schatz?

I'm sorry.

DR. LIMB: So getting to your question

about the C1 inhibitor product. So the C1 inhibitor product reduces the frequency of attacks. I don't have that number in front of me right now. We don't have any comparative information of how this drug might possibly compare to that.

DR. RIEDL: Could I speak to that, please, because I know the data?

The C1 inhibitor product, with all due respect, the FDA slide is incorrect. The approved C1 inhibitor product is a plasma-derived product. It's not the recombinant product.

The plasma-derived C1 inhibitor product that was approved, that study showed it reduced acute attacks by 60 percent, but it's very clear that there are patients that continue to have acute attacks, even while receiving prophylactic C1 inhibitor.

DR. CALHOUN: Thank you.

Okay. Now, Dr. Schatz.

DR. SCHATZ: Again, trying to understand this big difference in post versus pre sample size

adjustment, time to treatment appears to affect effectiveness.

Has the time between onset of attack and treatment been compared in the post versus the pre sample size change?

DR. HORN: Yes. So we have just run that analysis and we showed this slide where there was a zero to two, two to four, four to six-hour cutoff and the six to eight-hour cutoff, showing that the first three groups had a similar response and the latter group had a similar response to ecallantide, but also a much higher placebo response.

So when we look at that analysis, there are some changes, some shifts within the first three groups, but a very similar proportion of patients in the pre -- in the 52 and the 44 were in the six to eight-hour treatment group.

DR. SCHATZ: So that distribution isn't really different in the two pieces.

DR. HORN: No.

DR. CALHOUN: Finally, Dr. Terry.

DR. TERRY: I wanted to ask a further question about EDEMA4 and the pre/post adjustment.

I noticed that in EDEMA3, compared to EDEMA4, there were more patients who had previously had ecallantide, and I assume that means then that they were in EDEMA1 or EDEMA2.

What I wanted to ask, then, about EDEMA4 is those six outlier placebo patients. I wanted to ask, were they part of prior studies or not?

DR. HORN: We have looked at the patients identified as outliers by the FDA and looked at the demographics of those patients specifically.

Slide up, please.

We have limited our evaluation to the five patients that were included in the final 44 patients and not included the sixth patient who was actually included in the first 52. But when you look at these patients -- it's a very busy slide, but if you look down, it's the fourth row up from the bottom.

It's prior treatment with ecallantide. You see two of these patients had received prior

treatment with ecallantide and three had not. The first patient ending in 03 had not. The patient ending in 02 had. And the patient ending in 05 had not. The patient ending in 06 had. The patient ending in 01 had not.

Similarly, we look, there are three females and two males. Looking at these patients, we can't find anything in their demographics that would suggest they would have a better or worse response to ecallantide.

The one thing we did note, that when you look at the number of symptom complexes present, that four of the five had more than one symptom complex, where, in the overall program, it's closer to half of the patients have a single symptom complex.

So that's one thing we have identified in these outliers. But in our analysis, whether or not you have one or more symptom complexes doesn't affect your response.

DR. CALHOUN: Okay. We're now going to move on to the questions, of which, as you've

heard, there are five. I want to review the voting procedures for the committee.

We will be using the new electronic voting system for this meeting. Each of you have three buttons on your microphone, yes, no and abstain.

Once we begin the vote, please press the button that corresponds to your vote. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. I will read the vote from the screen into the record and then we will go around the room and each individual who voted will state their name and vote into the record, as well as the reason why they voted as they did.

Now, just to clarify that a little more, the vote that you make on your microphone can be considered a provisional vote. The official vote will be the vote that you record when you speak your vote. And so if the debate or the arguments around the table as we discuss change your mind,

you are free to do that.

With that, we'll start with Question 1, which is to discuss the hypersensitivity and anaphylaxis data and provide recommendations for further evaluation, if necessary.

Dr. Adkinson?

DR. ADKINSON: So I thought I might take this point to share with the panel my own assessment of the hypersensitivity reactions and the implications for the future of this drug and then see where some of my other colleagues who are knowledgeable in this area may agree or disagree as a way of moving forward here.

It's clear, I think, to all of us that hypersensitivity reactions represent the major toxicity of this treatment, which otherwise appears to be helpful and efficacious, to some degree, in some patients.

And it's not surprising that this is a problem for this drug, because it is a foreign protein, a synthetic protein and has not been seen by the immune system before and, like other

foreign proteins that are used as drugs, will almost invariably produce an immune response in some patients who receive it.

I'm impressed, from the data that we've been shown, that this is a drug that is highly immunogenic compared to other drugs that infrequently induce an immune response. This drug seems to induce it quite frequently and I think that the estimates that we've been given are probably underestimates.

One reason for believing is a report of the IgE assay showing 13 percent response with IgE antibody, but only 1.6 percent response with a so-called neutralizing antibody, which presumably is the major immunoglobulin class IgG antibody.

I'm not aware of any exceptions that have been studied in existing drug products that are foreign proteins in which it is not the case that IgE antibody responses in the absence of IgG antibody responses are extremely rare and almost impossible to find.

So I think that tells us that this

screening assay for IgG is probably insufficiently sensitive to pick up all of those who are sensitized to the drug. That's just the immunogenicity aspect of it.

The fact that 13 percent make an IgE antibody response suggests that this is a pretty potent immunogen, considering the fact it's not delivered in a repository fashion or administered with an adjuvant. So like other drugs of this type, aprotinin being a well studied example, one can expect hypersensitivity reactions based on immunological sensitivity.

The dose response curve that we've been nicely presented with suggests that even with these insufficiently sensitive assays, we can project up to 60 or 70 percent immune response rate, suggest that that rate really may approach 100 percent if we had sensitive enough assays.

So this is a drug that's probably going to sensitize most patients who receive it repeatedly, and the chances of having an antibody response that can mediate a severe allergic

reaction depends on a number of factors, not the least of which is the frequency with which patients are treated.

So like for a bee sting allergy, many patients tolerate a single insect sting once a year. It's the year in which they get a second sting two months into the season that they have a severe anaphylactic reaction, because the preceding antibody response has not had a chance to attenuate.

We know, again, from drugs like aprotinin, that over time, when a product is not used, both the G and the E antibody responses go down and patients may be tolerant of the drug in the future.

But this is unpredictable in the case of HAE patients because their episodes are unpredictable and, therefore, there is a need I think to be able to assess the risk for these type of potentially life-threatening reactions in patients who are candidates for therapy at a particular point in time.

So I'm a little concerned about the use of this product without a very stringent risk assessment program that is able to identify at least some, if not most of the patients who are at risk for potentially seriously life-threatening and maybe even fatal allergic reactions.

And this should be possible, because we know what the cause of these reactions is. It's either IgG or IgE or some combination thereof and we can measure these things. So this is technologically within the capability.

The complexity comes with the biological variation and that's why there's no current correlation between seroconversion, for example, and these reactions that have been observed. But that doesn't mean that these aren't the causal pathways that are involved.

So I would encourage development of a risk assessment program that would enable patients who are candidates for repeat therapy with this product to have some type of assessment, which would help to eliminate from further treatment at

that time patients who are clearly at substantial risk for having an immunologically mediated serious reaction.

I'm a little concerned about the use of a re-challenge program to establish patients who are prior reactors as being able to tolerate a subsequent treatment with the drug if by re-challenge we mean just giving the patient who had a previous systemic allergic reaction one milligram of the protein subcutaneously and waiting to see whether they have anaphylaxis.

That's a very crude and, in my judgment, unacceptable way of risk assessment because it subjects patients to serious potential for harm just from the reassessment procedure itself. And I think we can do better than that over time by looking at the sero status or the skin test status of patients who are treated after multiple encounters.

The other thing that seems, to me, that is almost invariably going to be the case is that the frequency of these reactions is going to

increase with increasing usage of the licensed product.

So that the estimates we have today are likely to be much greater, both proportionately and in terms of absolute number, once this product is on the market for a number of years.

And so a proactive effort to get a handle on this risk and to minimize it is essential, in my mind, to coming up with a favorable risk-to-benefit ratio for the treatment of a given patient at a particular point in time.

DR. CALHOUN: Dr. Borish?

I'm sorry. Dr. Ballow?

DR. BALLOW: I agree with my colleague. I think we need to know a lot more about the nature of these IgE and IgG antibodies. A proportion of these reactions occurred with first exposure; is that correct? What proportion?

DR. ADKINSON: The way I read what we've been given, all but one of these acute reactions -- my reading of the literature, of the data we've been given, is that all but one of

these acute reactions occurred in patients who previously were treated.

DR. BALLOW: Who were previously treated?

DR. ADKINSON: Treated, yes.

DR. HORN: If we specifically look at the eight patients considered potential anaphylaxis, three of those have had prior treatments. One was on the fourth episode, one was on the sixth episode, one was on the 17th episode. The remaining have all been on first dose exposure.

DR. BALLOW: Okay. So with that information, then, or possibly, it means that there may be some cross-reactivity.

And again, it brings up the similar reactions that were reported in the New England Journal of Medicine with cetuximab, in which there was a regional difference in reaction rate, presumably due to some cross-reacting antigen that was occurring in these individuals who subsequently got this monoclonal antibody.

So I think we need a lot more study about the nature of the IgE and IgG antibodies and why

they're occurring, presumably, on first exposure.

DR. ADKINSON: I don't deny the usefulness of those studies, but I'm also unwilling to believe there's not a stronger correlation if we had adequately sensitive immunoassays for both G and E. I think we're underestimating the previous -- the antecedent immune response in the patients who have had acute reactions.

DR. BALLOW: The other question I wanted to ask was in this particular yeast, is there any other drug that's been formulated -- that's your question, I know. I'm, I stole it.

Is there any other pharmaceutical that's been produced in this particular yeast using similar recombinant technology?

DR. LEE: Kathy Lee, with the Food and Drug Administration. I'm the primary product reviewer on this drug.

Yes, there have been other products formulated with Pichia pastoris.

DR. BALLOW: What's the data with regard

to hypersensitivity or reactions?

DR. LEE: I can't really speak to that, because it's a variety of different molecules and it would be a matter of going through the data. And I'm not a clinician. I'm a biochemist. Sorry.

DR. CALHOUN: Dr. Borish?

DR. BORISH: I was, first of all, struck by the fact that five of the eight episodes occur on the first dose. The other thing that's, frankly, striking is that we're talking about IgE and IgG and there's no correlation with IgE and IgG with these episodes.

People have IgE and don't react. The people reacting don't have IgE, either by assay or skin test. I mean, to me, this is screaming anaphylactoid and anaphylaxis, which makes me think that I disagree somewhat with what Dr. Adkinson said, that this is not a hypersensitivity reaction.

Further exposure may, in fact, not increase the rate. What you see in the first dose

may be what you get with this drug.

Now, it's possible that there's preexisting IgE to excipients or yeast products that we need to pursue, although I think the IgE to those would have shown up in the assays and didn't. Maybe we need better assays.

But there are, frankly, to me, obvious reasons why there could be anaphylactoid effects. This is a protease inhibitor. It was designed to inhibit one specific protease, but you know there's off-target effects. I know of one off-target effects, patients' PTTs were prolonged.

That's not because it's blocking kallikrein. I suspect there are probably some proteases out there that might be connected to some ITIMs on the MASO. Maybe Dr. Chowdhury knows this field, I don't. But I suspect that we're seeing a pharmacological anaphylactoid effect and it may, in fact, not progress with further use.

DR. CALHOUN: Dr. Gruchalla?

DR. GRUCHALLA: Couldn't that be tested by basophile histamine release or a MASO assay of

some sort? Or maybe that's already been done for non-specific --

DR. BORISH: And I would just put in the record that doing that on the MASO would be a totally appropriate request.

DR. CALHOUN: Do we have summary of recommendations then that we can give to the agency for what further needs to be done in terms of the evaluation of these immunologic responses?

DR. GRUCHALLA: One more point.

DR. CALHOUN: Rebecca?

DR. GRUCHALLA: One more point. Regarding back to one of your questions about the types of antibodies, you could do inhibition assays with various parts of the molecule to see if it's actually reacting to a certain part. So just, again, when you're doing those, do inhibition assays to get more information.

DR. CALHOUN: Dr. Ballow?

DR. BALLOW: So you are asking for recommendations about going forward, what kind of assays should be utilized?

DR. CALHOUN: I was just trying to crystallize specific recommendations to the agency that they could use in their planning process.

DR. BALLOW: I think some of them were stated before. I think you have to look at assays -- well, you have to improve on the basic assays of IgE and IgG, as Dr. Adkinson alluded to, and the other is to look at mediators.

I mean, tryptase is perhaps one, maybe some complement components, because if it's anaphylactoid, maybe there's evidence of complement activation as another possible pathway, and there may be other mediators that might be important.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: One more thing that may be worthwhile to start looking, and this is more of a potential hematologic thrombotic kind of concern, but to go ahead -- and because of the homology of the drug with the tissue factor initiator, perhaps getting studies for that, as well, in addition to the IgEs and the IgGs for the other components.

DR. CALHOUN: Dr. Schatz?

DR. SCHATZ: If one were to do immediate type skin testing routinely in a group of patients and if there were enough of them, one would get some idea then of the sensitivity and specificity of that as a predictive tool.

DR. CALHOUN: So that actually goes to Dr. Borish's comment that we don't know what the predictive value of a positive IgE serum, or positive IgG, nor skin test is for the manifestation of anaphylactic or anaphylactoid reactions to this agent.

DR. ADKINSON: I don't think I would state it that way. I think we do know that IgE is a risk factor for anaphylaxis and that we are administering -- we're talking about administering a foreign protein to a patient with an antecedent IgE antibody response.

There definitely is a substantial increase in risk of a systemic reaction. It's not 100 percent, but it's a finite number, and we're talking about life-threatening reactions here.

It's not trivial minor reactions.

We do know that's a risk factor. There may be other mechanisms involved, but it seems to me that when we're dealing with a foreign protein and we know is highly immunogenic, that we need to deal first with the immunologic reactions.

DR. FOGGS: Another long-term recommendation. Invariably, since these drugs come to market will be associated, as has been mentioned, with increased numbers of episodes of anaphylactoid or anaphylactic reactions, is establishing a prophylactic protocol akin to what we have utilized in association with radio contrast media?

I think a preemptive strike by establishing such a protocol as the data is generated will be most useful.

DR. CALHOUN: Okay. Next is Question 2. This is a voting question. It comes in two pieces. The adult piece is 2-A and the pediatric piece is 2-B.

So the question is do the data provide

substantial and convincing evidence that ecallantide provides clinically meaningful beneficial effect on acute attacks of hereditary angioedema in patients 18 years of age and older?

So you can vote your conscience at this point for 2-A, 2-A for the adults.

DR. PROSCHAN: Given that most of the analyses were done in the entire group, not separately for 18 years and older, to me, it seems like it might be a more useful question to ask, first of all, did they show benefit in this overall group, and then, secondly, is there sufficient evidence to make a separate conclusion or the same conclusion for the 10 to 17.

DR. CALHOUN: I don't disagree with you. The questions came from the agency and we need to give them advice, I guess, in the context of their structure.

Is that fair?

So again, this is Question 2-A, do the data provide substantial evidence of efficacy in patients 18 years of age and older?

At some point, these will be locked in. I guess as long as they're flashing, you can change your vote. There's one person who has not voted, apparently.

Do we have 18? Yes, okay.

The results are yes, eight; no, four; one abstention. That counts 13. I misspoke and said 18 earlier. There are 13 voting members. Sorry.

So, Dr. Hoidal, perhaps we can start with you and we'll work around the table.

DR. HOIDAL: John Hoidal. I voted no. This is a difficult decision for me, but in the end, I was concerned -- the issue of substantial and convincing, I didn't think the bar was met.

I was concerned of some uncertainty of overall efficacy and robustness of response, without an adequate explanation for the striking differences between the pre and post on the EDEMA4 study and without -- and with a fairly modest response in the EDEMA3 study with the switch of a couple of patients in terms of robustness.

DR. CALHOUN: Thank you.

Dr. Gruchalla?

DR. GRUCHALLA: I actually voted yes. I agree that the efficacy could be greater. However, I feel like the data was strong enough. I am concerned about the hypersensitivity issues and feel that in addition to looking at the efficacy issues, that the hypersensitivity issue needs to be evaluated over time.

DR. CALHOUN: And we will come to that with safety.

I neglected to ask each member to state their name and their vote prior to their comments.

Dr. Terry?

DR. TERRY: Peter Terry. I voted no. And the reason I voted no is, first of all, for EDEMA3, I didn't consider it robust when the change of two patients could make that much statistical difference.

And for EDEMA4, the extension seems to be so much different in terms of distribution of clinical presentation and these unusual outliers, that I'm not convinced that it would be

representative of a much larger sample.

DR. BORISH: Lawrence Borish. I voted yes. For an orphan disease, I don't think we're ever going to enroll enough patients to generate enough statistics to robustly satisfy every objection that can be raised.

My teaching in statistics is that you pick a primary aim, you pick a statistical plan, you do it and you live and die by your primary aim. We don't do retrospective analyses of secondary and tertiary endpoints or subgroup analyses, nor do I think should we do that in our statistical analysis. They met their primary aim and I voted yes.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: Paula Carvalho. I also voted yes. And again, I echo Dr. Borish's comments. Again, with an orphan disease, this is a tough one and this is also not a minor inconvenience. This is a very deadly condition. And 18-year-old and older is very similar, in my mind, to an adult.

Also, these are the people that are going to be either within the end of puberty, within some of the risk factor times in their lives in which some of these events may be accelerating. So I voted yes.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: I voted no. I don't think it met the criteria.

If I had been asked does it show any efficacy, I probably would have voted yes, but substantial -- I forgot the exact wording, but I was not convinced, because especially in EDEMA4, if you look at the pre-group before the extension, the response to the drug was similar in both groups, but it was the shift in the placebo group that really created that statistically significant effect.

And there were an awful lot of -- on the data plot, there were an awful lot of patients that had response on placebo and there were also patients who were in the active treatment group that had minimal response. So it was not

convincing to me.

DR. CALHOUN: Dr. Adkinson?

DR. ADKINSON: Franklin Adkinson. I voted yes. I thought that the criteria for efficacy was acceptable and voted yes because I'm not convinced that additional studies or larger numbers are going to change this relatively weak effect for a very complex disease.

DR. CALHOUN: I'm Bill Calhoun. I voted yes. This is an orphan drug for a rare disease. So echoing Dr. Borish's comments, I think that it will be logistically and practically very difficult to do a study that would provide definitive, substantial and convincing efficacy.

EDEMA3, the reason I asked the question I did about how and when the error was detected was had the error been detected sometime down the line, I would have been substantially skeptical, but this was really a technical violation, not really even a misrandomization. It was really a technical error, a clerical error.

And so I think, in fact, the analysis by

treatment was proper and the intention to treat is, in fact, in this case, not the right way to analyze the data.

On EDEMA4, I am intrigued scientifically by the variation between the first and last groups of patients. Collectively, the study is convincing to me.

The post hoc analysis I think probably raises lots of very interesting biological questions, which absolutely need to be addressed, and I think the questions of immunogenicity that Dr. Adkinson raised, the issues of dosing that Dr. Borish raised are very important. But collectively, I think EDEMA4 is a strong study. So I voted yes.

Dr. Schatz?

DR. SCHATZ: Well, obviously, I found this decision difficult. I couldn't make it. But my abstention is pending further evaluation of the current data. It's clear that the need is overwhelming.

But still the question of efficacy or

effectiveness, which seems, to me to be, as you can tell from my other questions, so much related to the difference in the second study, between the second phase and the first phase.

I think that, number one, looking at the symptom scores with just three levels instead of five would be useful and I certainly would like to see a relationship of effectiveness to baseline C1 esterase inhibitor levels before, then, I would be able to answer this question as to whether I think enough of an effectiveness burden has been shown.

The need is overwhelming, but we do need to be able to show that it's an efficacious medicine.

DR. CALHOUN: Dr. Ballow?

DR. BALLOW: Mark Ballow. I voted no, mainly because I'm really bothered by EDEMA4 study between the difference -- between the pre and post sample sizes.

There has to be an explanation. In fact, if we were going under Robert's Rules of regulation, I would have voted to table this whole

notion until we got better information back, perhaps an analysis like Dr. Borish proposed, looking at the C1 esterase inhibitor functionality and trying to correlate that with response.

At this point, for me, it's really difficult to tell about efficacy because I' really bothered about the two sets of data between the pre and the post sample size.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: Richard Honsinger. I voted yes. We have a drug that's less than perfect, does not always work, has problems with hypersensitivity, but it's the only thing we have for this orphan disease and it looks like, at least some of the time, it works.

DR. CALHOUN: Dr. Foggs?

DR. FOGGS: Michael Foggs. I voted yes. I think it's been pointed out time and time again during this session that there is a compelling need for acute treatment for hereditary angioedema and even though this treatment is less than perfect, I think on a compassionate basis, I was

personally obligated to vote yes.

I'm somewhat impressed by the fact that of those patients who did respond, greater than 50 percent of them responded within a two-hour period, and certainly, that's comforting for those patients who are experiencing flares of hereditary angioedema.

I would like to have seen better data and more data, but because of the reasons so stated, I voted yes.

DR. CALHOUN: Dr. Proschan?

DR. PROSCHAN: Michael Proschan. I voted yes. This was really close for me. And I really am voting yes on the question that I said, which is, was there an effect in the overall group.

By far, the thing that bothered me the most was the pre/post difference in the fourth study and, I mean, that's a big difference. And the FDA's analysis showed that there was a treatment by time pre and post interaction.

That was using a test that's harder to find an interaction. If they had done something

with continuous outcomes, it might have come out even more striking.

But I don't think the company did anything nefarious. I think they probably just ran out of the very sickest patients and then the next group of patients is less sick and for some reason, the treatment does better in those.

So I'm convinced by that analysis that this treatment helps some people. If the treatment didn't help anyone, then even if they had done something nefarious, they couldn't have made it come out significant.

The imputation didn't bother me quite so much because I do think it makes some sense to do the imputation they did. Even though it came out making the drug look better, I think that might be a fair thing to do if it is preventing additional emergent events.

The two given the wrong treatment, I mean, in a small study like this, if you switch the labels of patients, then, of course, it's likely that it will change the results. So I

agree that it's not a robust result, but I don't think you can really get a super robust result with the numbers of patients that we're talking about.

Then the last issue, the number of tests issue that you brought up, it does bother me that sometimes they present a pooled analysis, while sometimes they present the separate results, and then they also presented an analysis stratified by certain things which made it look even better.

But there I think the company made a mistake in not making the primary analysis stratified anyway. When you stratify the randomization, the sensible thing to do is also to stratify the analysis in the primary analysis.

So it wasn't strong, to me, but it was enough to tip the scales for me.

DR. CALHOUN: Okay. That concludes our vote on Question 2-A.

Dr. Hendeles, you have a comment?

DR. HENDELES: I just made the observation that most people voted what they

thought the agency should do, not what the question was.

The question was, is whether it has substantial and convincing evidence. If you listen to what everybody said, they -- well, I just think they changed the question.

DR. CALHOUN: Point taken. With that, we'll move to Question 2-B.

Do the data provide substantial and convincing evidence that ecallantide provides a clinically meaningful beneficial effect on acute attacks of hereditary angioedema in patients 10 to 17 years of age? Once again, your options are three; yes, no and abstain. And perhaps you can let us know when we have 13 rung in.

Okay. This time, we'll start at the other end of the table. Dr. Proschan, you're first.

DR. PROSCHAN: I voted no simply because I don't believe that with this amount of data, you can really separate out and say, okay, in this group of 10 to 17, there was a differential

effect.

So I can't tell whether, in that young group, there would be a different effect or not. So they didn't show convincingly in that subgroup, but I don't think they would be able to do that.

DR. CALHOUN: Dr. Foggs?

DR. FOGGS: I voted no for the age group of 10 to 17 because the limitations of the data were too great. I think that there were some convincing data with the 18 and over group. Even though it was not extremely convincing, it was somewhat convincing. I cannot make that statement about the 10 to 17 age group.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: Richard Honsinger. I voted yes. It's going to be difficult to collect children and children's data. Children often don't get diagnosed early. They often don't show up with the disease until their mid or their late teens.

It's going to be difficult to collect that data. And I have no reason to think that

children are any different in this disease than adults and that their response should be any different than those over 18.

In addition, these people have no other therapy. We're talking about a drug that has a very short half-life, a very short action, and I agree that the company needs to and should be compelled -- if released for children, should be compelled to collect data, when it can, on children's use of this drug.

DR. CALHOUN: Dr. Ballow?

DR. BALLOW: Mark Ballow. Responding to the strict wordage of the question, there is not enough -- there is obviously not enough data to substantiate efficacy.

DR. CALHOUN: Dr. Schatz?

DR. SCHATZ: Michael Schatz. I agree it's a different question as to whether we would expect that group to respond any differently, but I would have to agree the data are not adequate to show it.

DR. CALHOUN: Bill Calhoun. I also voted

no. There were four children in randomized double-blind placebo-controlled studies, which is not enough data to be convincing nor compelling.

Dr. Adkinson?

DR. ADKINSON: Franklin Adkinson. I voted no, based entirely on the numbers.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: I voted no, but; no, based upon the question, but I think the response would probably be the same in that age group.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: I voted yes. I ignored the verbiage of the question and I went with what I would actually do if I were faced with a child in the emergency room. I would find it difficult. As Dr. Honsinger said, there are not going to be that many of them and I would hate to have an age cutoff in which I was not allowed or able to give a potential medication for a kid.

DR. CALHOUN: Dr. Borish?

DR. BORISH: Lawrence Borish. I voted yes. If 10 to 17 is an orphan indication within

an orphan disease, if we are asking the industry to come up with compelling data in 10 to 17 year olds, it will never happen.

Hereditary angioedema in adults and hereditary angioedema in adolescents is the same disease. There is no conceivable reason why a drug that we agree works in adults won't work in adolescents and we have numbers of patients who support that concept.

It is conceivable that perhaps some of us can use it off-label, but I suspect it will take an act of God to get an insurance company to approve an off-label indication. So I voted yes.

DR. CALHOUN: Dr. Terry?

DR. TERRY: I voted no because I literally interpreted the question that we're being asked. I think the data is inadequate.

DR. CALHOUN: Dr. Gruchalla?

DR. GRUCHALLA: Rebecca Gruchalla. I voted no for the same reasons, for the numbers issue, but I totally agree with Larry Borish. I mean, if the question had been worded differently,

I would have answered yes.

DR. CALHOUN: Dr. Hoidal?

DR. HOIDAL: John Hoidal. I voted no, for the reasons stated of inadequate data.

DR. CALHOUN: Okay. Thank you, Committee, on Question 2.

Dr. Borish and Dr. Gruchalla, I think perhaps at the end of the questions, you could be prepared to articulate something in terms of advice or guidance to the agency along those lines. I happen to agree with you, personally, on the orphan indication, but on the basis of the question itself.

Our next question is also a voting question. It's also a two-part question. Question 3-A is, "Has the safety of ecallantide been adequately addressed for the treatment of acute attacks of hereditary angioedema in patients 18 years of age and older?" Three choices; yes, no and abstain.

So we have one not voted? Okay, we're there?

The results are five yes and eight no.

Dr. Hoidal, can we begin with you?

DR. HOIDAL: I voted yes, which is a little tough. It was based on the data that was presented in terms of safety, it was based on the safe use program that was outlined, and it was based on the suggestions that have already been forwarded in terms of the major side effect.

DR. CALHOUN: Dr. Gruchalla?

DR. GRUCHALLA: Rebecca Gruchalla. I voted no. All I am saying here is that I think it needs to be continually explored and the various assays that we discussed previously employed.

DR. CALHOUN: Dr. Terry?

DR. TERRY: Dr. Terry. I voted no, because of my concern that we haven't developed a refined method of predicting those who would likely be at risk for anaphylactic or anaphylactoid reactions.

DR. CALHOUN: Dr. Borish?

DR. BORISH: I defined adequately assessed as assessed adequately to balance the

risks of the un-safety of this drug with the risk of this disease. The public testimony was very, very moving in terms of the fact that patients are dying every year of this disease. We can treat anaphylaxis. We can't treat HAE. I think the safety is adequately addressed.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: I also voted yes. This drug is only to be given in a monitored setting. It's not to be given by self-injection like some of the other agents that patients have available to them at home.

For that reason, as long as we're aware of the potential adverse effects, then we should have something in place for us to be able to treat them, and we can treat anaphylaxis in the emergency room.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: I voted no, but, again, I don't think the data is adequate, but I think there's enough to approve the drug. And it reminds of the situation with Xolair, where there

was a signal in the original package that expanded with use. And so I just think there needs to be some post-marketing monitoring program to collect that information.

DR. CALHOUN: Dr. Adkinson?

DR. ADKINSON: I voted no. I continue to be concerned about the risk management program proposed by the sponsor as being inadequate to identify those patients at highest risk for what could be a fatal outcome, which I think is not an acceptable side effect for this drug.

DR. CALHOUN: Bill Calhoun. I voted yes. The safety data are adequate. I agree with Dr. Adkinson and Hendeles and others that it is not optimum. It's not complete. It's not where it needs to be. But it's adequate to at least know where we need to be looking for a safety signal as we go forward.

Dr. Schatz?

DR. SCHATZ: Michael Schatz. I hope people understand that people are saying exactly the same thing, but with different votes.

Again, it depends on what's adequate. I think it's not adequate to understand everything we'd like to know about it. It may very well be adequate to balance the potential benefits. But that's not how I interpreted the question. So I voted no.

DR. BALLOW: Mark Ballow. I voted no. I agree with Dr. Schatz in what he said.

The other thing -- now, don't take it as self-evident that medical centers know how to treat anaphylaxis. Many times, they don't satisfactorily treat anaphylactic or anaphylaxis.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: Richard Honsinger. I voted yes. The question asks if the safety has been adequately assessed. I think we assessed the safety. We found out the drug does have a problem of hypersensitivity.

We assessed the drug for cardiac effects with its QT. We assessed it for thrombosis. We assessed it for renal and hepatic effects and did not find other serious effects with this drug that

has such a short action. So I voted yes.

DR. CALHOUN: Dr. Foggs?

DR. FOGGS: I voted no because I think some of the studies that need to be done have been carried out, but to a limited degree.

And I think the immunology is sufficiently complex that additional studies need to be done to eliminate the potentially excessive risks, especially as the drug comes to market, for individuals succumbing not only from anaphylaxis, but also from possibly other problems associated with the use of this drug which have not been explored yet, such as the absence of coagulation studies mentioned earlier.

DR. CALHOUN: Dr. Proschan?

DR. PROSCHAN: Michael Proschan. I voted no. I guess I'm looking to Question 4 as far as the balance of the safety and efficacy. So I voted no.

DR. CALHOUN: Okay. That concludes voting on Question 3-A.

Dr. Adkinson?

DR. ADKINSON: I voted no, in part, also, because I believe that the potential for creating a hypercoagulable state as a result of the antibodies produced by this product needs to be definitively assessed, and that has not been done. I would not make that a precondition for approval, but I do think it's a safety issue that has not been addressed that needs to be.

DR. CALHOUN: Okay. Thank you.

So Question 3-B is, "Has the safety of ecallantide been adequately addressed for the treatment of acute attacks of hereditary angioedema in patients 10 to 17?" Question 3-B.

Okay, pause. Dr. Hendeles?

DR. HENDELES: Would the agency be willing to remove the words "substantial and convincing" from that question?

DR. CALHOUN: "Substantial and convincing" are not in 3-B, right?

DR. HENDELES: No, four.

DR. CALHOUN: We're on 3-B.

DR. HENDELES: Oh, I'm sorry.

DR. CALHOUN: That's okay. You can be embarrassed a second time.
DR. HENDELES: Shut my mouth.
DR. CALHOUN: Okay. So we're voting 3-B, the safety in children 10 to 17.
We have one vote to come in?
Okay. We have 13?
For the record, two yes, 11 no, and zero abstentions.
I guess we're back to Dr. Proschan.
DR. PROSCHAN: Michael Proschan. I voted no. Given how I voted on the previous question, it would have been absurd for me to vote any other way, and given that we know less about the 10 to 17 group.
DR. CALHOUN: Dr. Foggs?
DR. FOGGS: My reason for voting no is the same for the 18 and over group.
DR. CALHOUN: Dr. Honsinger?
DR. HONSINGER: Richard Honsinger. No, because we do not have any data, but I don't think that this should withhold the drug from market.

DR. CALHOUN: Dr. Ballow?
DR. BALLOW: Mark Ballow. No, for the similar reasons for part A.
DR. CALHOUN: Dr. Schatz?
DR. SCHATZ: Michael Schatz. No, for everything that's been said.
DR. CALHOUN: Bill Calhoun. No. Total experience of 15 patients.
Dr. Adkinson?
DR. ADKINSON: No, ditto.
DR. CALHOUN: Dr. Hendeles?
DR. HENDELES: Leslie Hendeles. No.
DR. CALHOUN: Dr. Carvalho?
DR. CARVALHO: Paula Carvalho. Yes, for the same reasons as before. Although the numbers may not be there, the concerns, we are well aware of the concerns that we have and my yes is on a philosophical rather than on the verbiage.
DR. CALHOUN: Thank you.
Dr. Borish?
DR. BORISH: Lawrence Borish. Ditto.
DR. CALHOUN: Dr. Terry?

DR. TERRY: Dr. Terry. I voted no, for the reasons stated.
DR. CALHOUN: Dr. Gruchalla?
DR. GRUCHALLA: Rebecca Gruchalla. I voted no, for the reasons stated.
DR. CALHOUN: And Dr. Hoidal?
DR. HOIDAL: John Hoidal. I voted no, for the reasons stated.
DR. CALHOUN: Thank you. That completes our voting on Question 3.
Question 4 is the last voting question and it goes to the point that Dr. Proschan has mentioned a couple of times. It's the balance between safety and efficacy.
Please note. Please note that this question does not split into adults and pediatric age ranges. This is a question that's based -- correct me if I'm wrong, Badrul. This is a question based on the proposed label submitted by the sponsor.
DR. CHOWDHURY: Yes, that is correct.
DR. CALHOUN: Thank you.

I have not personally seen the label, but this is based on their proposed indication. Correct?
DR. CHOWDHURY: That is correct. It is based on the proposed indication, which covers the age ranges down to 10 years of age.
DR. CALHOUN: Okay. Thank you.
So Question 4, again, a voting question, "Do the safety and efficacy data provide substantial and convincing evidence to support approval of ecallantide for the treatment of acute attacks of hereditary angioedema?" Three choices; yes, no and abstain.
So a point of order and a question to the agency, which --
Les, do you want to just articulate what you're suggesting? I don't know to the extent they'll be willing to do that, but you certainly can make the statement.
DR. HENDELES: In question number 4, would you be willing to delete the words "substantial and convincing?"

DR. CHOWDHURY: As the chair mentioned, we will not be, because that is the standard based on which we take a decision whether to approve a drug or not. Be it the orphan indication or not, there has to be substantial and convincing evidence for us to approve a drug.

But keep in mind, you should be voting based on the question the way it is asked, but, again, you can make your comments later on. And for us, it is equally important to hear what you have to say and we take the comments very seriously as we talk about the drug internally for ultimately decision-making processes.

DR. CALHOUN: Thank you, Dr. Chowdhury.

Okay. So we'll vote Question 4. Please let me know when we have 13.

Okay. For the record, we have six yes votes, we have five no votes, and we have two abstentions.

And we'll begin with Dr. Hoidal.

DR. HOIDAL: I voted no, for the issues earlier expressed regarding the strength of the

data supporting efficacy, the lack of adequate studies in the pediatric population, and the concerns that have been raised about the adverse effects, particularly the anaphylaxis.

I would say that's not to say that the standard may be difficult to change or things may be modified in terms of an orphan drug indication.

DR. CALHOUN: Dr. Gruchalla?

DR. GRUCHALLA: Rebecca Gruchalla. I voted yes. I believe that the efficacy data, again, needs to be strengthened, but, again, this is an orphan disease, a bad disease, and I think the endpoints were met. I do believe that the safety issues need to be continually addressed as you move forward, but, again, I still believe that efficacy outweighs safety.

DR. CALHOUN: Thank you.

Dr. Terry?

DR. TERRY: I voted no, because that's consistent with my prior two votes for safety and efficacy. And I also don't believe that we should have a different standard for evidence related to

orphan diseases as any other disease.

DR. CALHOUN: Dr. Borish?

DR. BORISH: Lawrence Borish. I voted yes, because I considered the data, that it worked, compelling and I considered the safety concerns mitigated by the severity of the disease.

DR. CALHOUN: Dr. Carvalho?

DR. CARVALHO: Paula Carvalho. I also voted yes, for the same reasons that have been mentioned here before. This is, to me, a little bit different.

This is an orphan disease and I know that we have to be held to stringent criteria, but we have very little to offer this in this disease and we are fully aware of the dangers that could potentially exist.

I suspect that we'll be looking at those very aggressively. I echo Dr. Gruchalla's comment about that is a must for us to be able to, with a clear conscience, use this agent on people. But my vote was yes.

DR. CALHOUN: Dr. Hendeles?

DR. HENDELES: Leslie Hendeles. I abstained because I couldn't honestly respond to the question the way it was worded. But I believe that there is enough evidence of efficacy and safety and given the compelling need for this drug to provide it, but there needs to be -- and I'll address that later -- the precautions. It shouldn't be administered in a CVS pharmacy.

DR. CALHOUN: Dr. Adkinson?

DR. ADKINSON: Franklin Adkinson. I voted no, jointly taking into consideration the modest efficacy of this therapeutic product combined with substantial toxicity, which I think has not been minimized by an adequate risk management program.

DR. CALHOUN: Bill Calhoun. I voted yes. Again, this is an orphan disease. I'm not convinced that there will ever be truly compelling and convincing data generated. The safety concerns that have been articulated are real, they're important, and they cannot be forgotten.

And I think each of the "yes" voters has

mentioned that. So, Dr. Adkinson, you're right on the mark there.

However, we can treat anaphylaxis, particularly when the drug is provided in a medically supervised setting and, as we've heard, again, very eloquently from the patient representatives, without this drug, people may die.

Dr. Schatz?

DR. SCHATZ: I abstained, again, for similar reasons as before. I would like to see some additional data before I would want to judge the data. Initial analysis, I should say, as substantial and convincing, I don't think I can say it was substantial and convincing based on what we have so far.

But a combination of seeing additional data and still asking a different question, which is do the benefits outweigh the risks, that's still a different question, to me, than would I recommend approval. But I have to abstain based on the information I have so far.

DR. CALHOUN: Dr. Ballow?

DR. BALLOW: Mark Ballow. I voted no. It's a difficult ethical question. I certainly appreciate the fact that this is a difficult disease to treat. It's an orphan disease and not very many patients.

However, we've heard a lot of discussion around the table about difficulty with efficacy and, also, with potential adverse events and I think we cannot lower the bar. The FDA has gotten into trouble before by lowering the bar and it's come back to haunt them.

Hopefully, if this drug does not get approved at this particular time, there ought to be other ongoing studies with this particular medication so it will be available to patients.

There was a recent approval by the FDA of another "medication," quote-unquote, for use in this disease, although it's not for this particular indication, for acute onset of attacks, I imagine what will happen, if push comes to shove, that it'll be used off-label in a dire

situation where a patient's life is at stake.

But I really believe we cannot lower the bar, that we need some additional information. There's a lot of discussion about the shortcomings of this study and it needs to be cleaned up.

DR. CALHOUN: Dr. Foggs?

I'm sorry. Dr. Honsinger? I'm sorry.

DR. HONSINGER: Richard Honsinger. I voted yes. I voted yes because I believe this drug -- we have enough evidence to say that it's efficacious. We have problems about the safety, but I'm convinced that for an orphan disease, it could be fatal, and we need the drug.

DR. FOGGS: Michael Foggs. I voted no. The precise wording of the question by the FDA actually defines the standards set by the FDA and, to that extent, has been stated. An honest response to that particular question as it relates to the standards set would have to be no.

However, if I had the opportunity to separate out the age brackets between the 10 to 17 and 18 and over, I would vote yes, because I think

the efficacy is sufficient in the upper age bracket as opposed to the lower age bracket, even though I'm not satisfied with the safety for either age bracket.

DR. CALHOUN: Dr. Proschan?

DR. PROSCHAN: Michael Proschan. I think it's more accurate to say that I voted "you know" as opposed to yes. Yes, slightly ahead of no as opposed to the other way around.

It was very close, but I think that in this situation, when there's no other drug that treats it, I do think that they showed some efficacy and I have concerns about safety and, for me, it was just tipped more toward saying yes.

DR. CALHOUN: Okay. Thank you. So that concludes the voting on Question 4.

The last question before us, number 5, is a discussion question, asking our collective advice on recommendations regarding labeling, risk mitigation strategies for hypersensitivity and anaphylaxis, the potential for self-administration, and any other recommendations

you've got for the agency.

Dr. Hendeles, then Dr. Borish.

DR. HENDELES: I think it needs to have a strong precaution that clearly states that it should only be administered in a medical facility where there is personnel and equipment trained and experienced in handling anaphylaxis.

You laughed when I said CVS, but last night, I went to get a candy bar and there's a minute clinic in the CVS here where there's a nurse practitioner that sees patients for a fee. So that type of thing could happen, and so I think it really needs to be something close to an emergency room facility or an allergist's office.

DR. CALHOUN: Dr. Borish?

DR. BORISH: While I agree, in principal, while I will request all my HAE patients to have their episodes between the hours of 8:00 and 5:00 Monday through Friday, they're not always that cooperative.

In the 200-year history of the University of Virginia, I don't think any patient has been

seen in the emergency room in less than six hours who had a pulse and I don't see that changing.

I think patients with HAE will spend most of their time trying to convince the ER physicians not to give them Epi and Benadryl and to actually give them this drug. I think in the real world, they're going to get so impatient with the lousy service they get in emergency rooms, that we're going to have to find a way to get this drug administered at home.

As Dr. Riedl said very well, these patients are driven, they're motivated, they're intelligent, they know their disease. They can be taught how to treat anaphylaxis at home.

DR. CALHOUN: Dr. Schatz?

DR. SCHATZ: Relative to anaphylaxis, relative to the risk mitigation, again, I feel like a program that evaluates skin testing and the potential for pretreatment if, in fact, it's not -- some of these reactions are not IgE mediated, would help with risk mitigation over time.

More immediately, the education of the patient in the administration of self-administered epinephrine would certainly be appropriate and I'm sure would happen.

DR. CALHOUN: Dr. Honsinger?

DR. HONSINGER: Yes. I agree with the labeling. The labeling needs to warn about anaphylaxis. It's going to be difficult for these patients to get to the place, and Dr. Riedl told us about his case where the patient didn't have access to the medicine and had a serious outcome.

So I would think that it's something the patient may well carry and needs to go to a facility that can treat anaphylaxis to take their injection.

So it might be any place that's familiar with giving injections to patients that are at high risk of anaphylaxis. That's certainly the allergist's office. It certainly can be many urgent care centers, if you can get in.

It certainly can be in an emergency room, where you can actually take it while you're

waiting in the emergency room and then you're there for several hours to make sure if you have anaphylaxis, you'll be seen.

I think that we need to work to develop, challenge protocols and ways to evaluate it, whether it be skin tests, whether it be laboratory tests, for the patients that may be sensitive and we need to work on what we can do for those sensitive patients as far as prophylactic therapy when they receive the drug.

DR. CALHOUN: Dr. Foggs?

DR. FOGGS: I agree that with regards to labeling, all the patients who are administered the medication should have auto-injectable epinephrine at their disposal and be taught properly how to use it, should it be needed.

With regards to risk mitigation, I feel strongly that there needs to be a protocol established as these studies are being carried out to allow for assessment post-anaphylaxis in a systematic fashion so that data can be generated to help define what the reaction is and, also,

protocol be set up for potential prophylaxis once patients can be targeted, based upon biological markers or other markers, to identify their high risk for anaphylaxis as a result of taking this medicine.

DR. CALHOUN: Dr. Gruchalla?

DR. GRUCHALLA: I just have a question.

These are one cc injections, subcue injections, right? So trying to get those to be -- a patient to do that to themselves -- I mean, three. That's what I'm saying.

Could you do three one -- I mean, I'm just asking the question.

DR. BORISH: If I'm not breathing?

DR. GRUCHALLA: I mean, again, I'm not saying let's not move towards that, absolutely, but just in concept, because the EpiPen itself is how much? I don't know how much is in an Epi. It's a total of .3.

DR. BORISH: But this is subcue.

DR. GRUCHALLA: But anyway, it's just something to think about.

DR. CALHOUN: So a point of data perhaps for the industry, for the sponsor. Is there a solubility concern here? Is 10 milligrams all you can get into one ml or can it be made in a more concentrated solution?

DR. PULLMAN: We've actually been actively investigating the solubility issue. It's the solubility versus stability tradeoff. So that's why you have the 10 milligrams per ml. But it looks very feasible that we can push upwards in terms of the concentration probably to 30 milligrams per ml. That work is ongoing with external academic centers helping us.

DR. CALHOUN: And so at that point, you could get away with a single injection.

Dr. Honsinger?

DR. HONSINGER: I'd like to ask the industry about stability of this drug. And you mentioned that this drug can be kept out at room temperature for some time and then put back in the refrigerator.

How many times can it be done? What's

the shelf life of this drug? Is it months or is it years?

DR. PULLMAN: Actually, we recommend it be kept under refrigerated conditions, namely, two degrees to eight degrees. We do have stability data at room temperature that shows the product is within acceptance criteria for up to two weeks.

And we have done some cycling, I think cycling from refrigerator to room temperature about five times, and it still has integrity. But we recommend refrigeration two to eight.

DR. BALLOW: (Off mic) Expiration date?

DR. PULLMAN: There is at least two years stability for the refrigerated moiety.

DR. CALHOUN: Okay.

I'm sorry. Dr. Borish?

DR. BORISH: Just one quick comment under D.

If the drug does gain approval, one of the things I would like to see is a post-marketing study in Type III HAE, which is a disease -- as bad as the drugs are in HAE, none of them work in

Type III.

It's a real disease. I, at this point, may have as many patients with that as I do with Type I and II. And for those who know the disease, this should be effective there and I would love to see a post-marketing study in that disease.

DR. CALHOUN: Dr. Adkinson?

DR. ADKINSON: I just want to say what I've already said in another way. I think the best approach to maximizing the safety of this product is prevention, not learning how to treat anaphylaxis.

And I believe it's within our technical capability of the company and the FDA to assure essentially -- to eliminate, virtually eliminate all IgE dependent anaphylaxis to this product with proper pre-use testing. And that seems, to me, to be achievable and we should do it.

DR. CALHOUN: Okay. I'm going to give you a summary of what I've heard from this discussion and then I will invite comment and

edits from the committee.

So summarizing, I think we all have -- first, to say, were we the Supreme Court, Nina Totenberg would talk about a sharply divided decision.

In fact, I don't think this was a sharply divided decision. I think this was a unimodal population of opinions in which people came down on different sides of the dichotomous question. But there was quite a bit of homogeneity, I think, of discussion. We just read the issues a little bit differently and voted a little differently.

So I don't think you should look at the six to five to two decision as being that the committee couldn't make up their mind. I think you've heard the discussion. I think the committee has given you their advice.

So summarizing, I think we've heard that there are some concerns about the relatively modest efficacy, the lack of robustness of the findings. And so to the extent that additional can be brought to bear on that question, that

would be helpful.

Dr. Hendeles raised the point about perhaps improving the experimental design to make more of the same -- or make more of the patients that we've got access to.

There has been considerable discussion about the variable response by population, this first 52 versus last 44 issue, and I think the consensus that I've heard is that all of the committee members would like an intensive digging into the biology that underlies that variability.

And there may be some bio samples in a bio bank at the sponsor's area. The agency may well have information in their database that they can search through. But I think trying to understand that difference between those two populations would be extremely important.

I think we saw by the vote that the majority of the committee was unconvinced by the amount of data that were provided. So as things go forward, given all of the considerations that Dr. Borish articulated in this regard, the

difficulty of generating real information in pediatrics, to the extent that it can be done on the way forward, I think that's certainly a recommendation that the committee would make.

There are a number of safety concerns. Dr. Adkinson has articulated these very, very elegantly. The coagulation issues, I think have, in fact, not been addressed at all. The anaphylaxis issue we've talked about quite a bit.

I just will say, personally, Frank, I don't know that there's debate about what you said that we ought to prevent anaphylaxis. I think that's exactly right. If we can predict and prevent the anaphylaxis, that's exactly the right strategy.

So identifying predictors of adverse responses, whether that represents -- whether that can be accomplished with more sensitive assays for IgE and IgG or other predictors, but you really -- the company, the sponsor, needs a predictive biomarker for adverse events, because it is clear that anaphylaxis can kill, can and does kill,

maybe just as dead as if you die from an HAE episode.

So eliminating the anaphylaxis I think is certainly a priority.

So those are the distillates of the discussion that I've heard and I would, at this point, entertain any edits or amplifications.

Dr. Borish?

DR. BORISH: Is it a reasonable marketing -- is it an appropriate labeling request to ask the company to provide free screening for IgE for patients getting this drug? Because while Dr. Adkinson and I split slightly, I absolutely agree with him that if someone has IgE, you don't want to cavalierly administer the next dose.

And people who are getting this dose regularly probably should be screened regularly. It's not going to be available in any laboratory at my institute. The company really are the only people that can do it and, frankly, they should do it.

DR. CALHOUN: And to the extent that

there might be -- using your venom immunotherapy concept, Frank. The fact that you've got IgE positivity at one point may put one at increased risk, but I think that the predictive value of those tests needs to be ascertained in an objective and an empiric fashion.

Dr. Gruchalla?

Pardon me. Dr. Chowdhury?

DR. CHOWDHURY: Thank you very much for the summary. It was actually very, very helpful for us to hear the comments on the voting and we really appreciate the comments that we have received and also your summary.

There's one point I would like to go back and perhaps encourage some discussions, if you could, because we have heard multiple times from Dr. Borish and Dr. Schatz about the C1 esterase levels as a predictive factor and we will certainly go back and look at it.

But the question that really we need to get a sense from the committee here is how strongly really the committee feels about the C1

esterase levels being predictive of severity of the attack. In other words, if the level is high, is that going to be more severe? If the level is low, is that going be less severe?

Secondly, how stable the C1 esterase level in a particular patient is going to be over time of the disease, because in many of these patients, the time that the C1 esterase levels were drawn in relationship to the drug administration may vary, because I don't think we have a very good handle, from a scientific literature standpoint, of the C1 esterase levels as predictors and we're certainly going to go back and look at it, but we would like to have some discussions around this issue, which would be very helpful to us.

Thank you.

DR. CALHOUN: Okay. Dr. Schatz?

DR. SCHATZ: Well, I was going to say a little bit different. But in answer to that, again, I don't think the company -- I mean, I think the company said that there isn't a

relationship between attack severity and C1 esterase inhibitor, but that's really not the question.

The question is whether there's a difference in responsiveness to the drug based on preexisting levels. So the second questions you asked are important. But that's the analysis that needs to be done and, to my understanding, that hasn't been looked at.

DR. BORISH: I was going to make the same comment, because I misspoke earlier and I want to be very clear. C1 inhibitor levels or functional doesn't predict severity or episodes or the nature of episodes or anything like that.

I was really wanting to speculate that maybe the patients with the lowest levels, that might predict a responder subgroup. So I want to correct my earlier remarks.

DR. HENDELES: Functionality, not whether --

DR. BORISH: Yes, functionality may predict response to treatment, not severity.

DR. CALHOUN: Dr. Gruchalla?

DR. GRUCHALLA: One other thing. I'm not sure how much the skin testing has been explored and does the skin test align with the in vitro IgE results. If they did -- again, I don't know if this is a nonspecific MASO releaser.

In that case, then the skin test is not going to be useful at all. But if it were not and it was specific IgE, that would be an easy screening assay, if, indeed, you could get it to work.

DR. CALHOUN: Dr. Hoidal?

DR. HOIDAL: Just kind of broaden that comment, because you have these striking differences and there's got to be some information there.

So just mining the information of all the biologic data, the phenotypic data and see if there's any predictors that you can come up with, because as we move forward, if you could save a substantial portion of non-responders from the risk of anaphylaxis, you'd do them a great favor.

DR. CALHOUN: Dr. Honsinger?
DR. HONSINGER: Maybe someone else can answer. I don't know that the variability of the C1 esterase inhibitor in a single patient -- we know they're low, but do they go high and low just like complement does? I think we need to also establish that before we hang our hat on that measurement.
DR. CALHOUN: Dr. Carvalho?
DR. CARVALHO: Just one quick comment for the sponsor. We've heard a lot of the patients tell us, and we've seen this ourselves, where people don't know what this entity is and patients come to the emergency room and they go through all of these things and time is wasted because this is not recognized. Many times, the patients know much more than the physicians about the disease.
I would urge the company to make a very, very, very massive educational effort throughout the emergency rooms for teaching hospitals, for community clinics, everywhere, because these patients are going to be out there.

And if there's something that can be offered -- it's almost going to be analogous to stroke issue with saving cerebral tissue with different treatments that are now available. So anything that's time-based and anything that has the urgency that this has needs a huge educational effort and I would encourage that.
DR. CALHOUN: Dr. Gruchalla?
DR. GRUCHALLA: Quick comment. Do they wear Medi-Alert bracelets? I mean, that would be -- I mean, the question is -- this is another thing I'm thinking, like mastocytosis patients that come to the emergency room and nobody knows about the disease.
What about Medi-Alert bracelets?
DR. CALHOUN: Is there a response?
DR. RIEDL: If I could have your permission.
DR. CALHOUN: Certainly.
DR. RIEDL: I don't want to speak for the patients, but I can tell you that in my practice, I care for about 30 to 35 HAE patients and we do

encourage medical alert bracelets.
The other thing that I do, which is variably helpful, is provide a letter that explains their condition and the treatments, which, up to this point, have been very little, but the treatments that may be available that they can take to the emergency room.
The other thing that we try to do at our center is establish a home emergency room where they frequently will -- as closest to their residence, that they will go to.
And with an emerging area of medical records, we're hopeful that, in the medical record, there will be a denotation that they have hereditary angioedema, and that would solve this battle that they fight day in and day out to convince people of this rare condition.
DR. CALHOUN: Okay. Perhaps, Dr. Chowdhury, I can ask you if there are other aspects that you'd like to hear additional discussion about.
Dr. Seymour, Dr. Limb?

DR. CHOWDHURY: No. We think we had a very good discussion around the issue that we wanted to be discussed and it was very helpful for us.
Dr. Seymour, Dr. Limb, Dr. Permutt, any other issues?
No, we don't. Thank you.
DR. CALHOUN: Okay. Well, with --
Dr. Hubbard? I'm sorry.
DR. HUBBARD: Yes. First of all, I'd like to thank you for an excellent session. And I don't mean to have the last word in a negative way, but as an industry representative, I do have a slightly different role than other folks here and I wanted to make sure I separated my comments from any consideration of ecallantide.
I just want to express my concern with the statistical approach to the analysis of the efficacy data, in particular, with the way the efficacy for E4 was analyzed.
I'm at a loss to understand why the agency was unwilling to accept the primary

endpoint that they agreed to beforehand and was discussed with the sponsor, why they failed to accept the analysis at its face value and went ahead and conducted additional analyses, which I think prejudiced the value of the primary endpoint, which was quite solid.

So I just think that it's important that I do express that on behalf of a sponsor. If you do the flip test and if we were to do something like that, I think it would be rowdily disputed and not accepted.

So I think it's just important for us to have an understanding of the rules by which you go about doing thorough post hoc analyses of efficacy data so that we can be prepared for this kind of thing should a sponsor come before the agency in the future.

DR. PROSCHAN: Could I address that?

DR. CALHOUN: Dr. Proschan? Yes.

DR. PROSCHAN: I mean, I think in this situation, it's a little bit different, though, because the original sample size was supposed to

be 52.

It's not like the original sample size was 96 and then they went back and said, okay, let's look at the first half and see if that's different from the second half. There is an issue when you decide to change something midstream, namely the sample size, there is a natural concern about it.

DR. HUBBARD: Yes, but, I mean, you agreed to this before they did it, I think.

You didn't?

DR. CALHOUN: Actually, Dr. Proschan didn't.

DR. PROSCHAN: I certainly didn't.

DR. CALHOUN: Just point of order --

DR. HUBBARD: My understanding is the agency agreed to this.

DR. PERMUTT: I have to make two points here. One, we agreed to the original protocol. We agreed to the amendment to the protocol with the condition that this analysis would be performed. So we are doing -- we are presenting,

in fact, what was agreed to.

Second, I think you've mischaracterized what we've done here. We haven't refused to accept the analysis. We're here asking for advice.

We think that this feature of what we observed in our analysis was relevant to the committee's deliberations and, clearly, many people on the committee also thought it was relevant and interesting and important. The decision has yet to be made.

DR. ROSEBRAUGH: Let me just add something, also. It is not unusual for us, much like the sponsor would do, to do a lot of sensitivity analysis. Additionally, when we come before a committee, we want them to have the full range of the picture and it would really be unfair of us to not present the full range of the picture to the committee and seek their advice.

As Tom just said, that doesn't mean we've rejected anything. We've done sensitivity analysis on a primary on a very small database.

That's very appropriate to do.

DR. CALHOUN: Dr. Terry?

DR. TERRY: Yes. I'd like to ask a question of Dr. Chowdhury.

Do you have expectations that orphan diseases as opposed to non-orphan diseases will be analyzed by different standards of evidence and do you have any sort of guidelines for that?

DR. ROSEBRAUGH: I'm not Dr. Chowdhury, but I'll take that. No, we don't. Orphan disease does not get a break. So they have to have the same level of evidence that we think it works. I mean, we really don't want to make a Type I error. We do not want to make a Type I error.

DR. CALHOUN: Okay. With that, I would like to thank the Dyax folks for their comprehensive presentation. Thanks to the FDA folks for their very, very detailed and insightful, informative analysis.

Thank you to the press for your interest. Thank you to the HAE Society and the other members of the speaking team, and many thanks to the

members of the committee.

We're adjourned.

(Whereupon, the proceedings at 3:19 p.m. were concluded.)