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4 FOOD AND DRUG ADMINISTRATION
5 CENTER FOR DRUG EVALUATION AND RESEARCH
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9 Pulmonary-Allergy Drugs Advisory Committee
10 Ecallantide for the Treatment of
11 Acute Attacks of Hereditary Angioedema
12 Wednesday, February 4, 2009
13 8:30 a.m.
14
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16
17 Hilton Washington D.C./Gaithersburg
18 620 Perry Parkway
19 Gaithersburg, Maryland
20
21
22

1 MEETING ROSTER
2
3 PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE VOTING
4 MEMBERS:
5 PAULA G. CARVALHO, M.D.
6 Director, Intensive Care Unit
7 VA Medical Center/Boise
8 500 West Fort Street
9 Boise, Idaho 83702
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11 MICHAEL B. FOGGS, M.D.
12 Chief of Allergy, Asthma & Immunology
13 Department of Medicine
14 Advocate Health Center
15 2545 S. Martin Luther King Drive
16 Chicago, Illinois 60616
17
18 RICHARD W. HONSINGER, M.D.
19 Los Alamos Medical Center Clinic, Ltd.
20 3917 West Road
21 Los Alamos, New Mexico 87544
22 (Roster continued on the next page.)

1 ROSTER (continued):
2
3 NON-VOTING MEMBERS:
4 RICHARD C. HUBBARD, M.D. (Industry
5 Representative)
6 Senior Director, External Medical Affairs
7 International Office of the Chief Medical
8 Officer
9 Pfizer, Inc.
10 235 East 42nd Street
11 New York, New York 10017
12
13 ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY
14 COMMITTEE VOTING MEMBERS:
15 MICHAEL PROSCHAN, Ph.D.
16 Biostatistics Research Branch
17 National Institute of Allergy and
18 Infectious Diseases
19 National Institutes of Health
20 6700A Rockledge Drive, Room 5140
21 Bethesda, Maryland 20892
22 (Roster continued on the next page.)

1 ROSTER (continued):
2
3 BLOOD PRODUCTS ADVISORY COMMITTEE (CENTER FOR
4 BIOLOGICS EVALUATION AND RESEARCH) VOTING MEMBERS:
5 MARK BALLOW, M.D.
6 Interim Chair, Department of Pediatrics
7 Chief, Division of Allergy & Immunology
8 Women and Children's Hospital of Buffalo
9 219 Bryant Street
10 Buffalo, New York 14222
11
12
13 TEMPORARY VOTING MEMBERS:
14 LAWRENCE BORISH, M.D.
15 Professor of Medicine
16 Asthma and Allergic Disease Center
17 University of Virginia Health System
18 Charlottesville, Virginia 22908
19
20
21
22 (Roster continued on the next page.)

1 ROSTER (continued):
 2
 3 TEMPORARY VOTING MEMBERS (continued):
 4 REBECCA GRUCHALLA, M.D., Ph.D.
 5 Associate Professor of Internal Medicine
 6 Department of Internal Medicine
 7 University of Texas Southwestern Medical
 8 Center
 9 5323 Harry Hines Boulevard
 10 Dallas, Texas 75390
 11
 12 WILLIAM CALHOUN, M.D.
 13 Sealy and Smith Distinguished Professor
 14 Vice Chair for Research
 15 Department of Internal Medicine
 16 University of Texas Medical Branch
 17 4118 John Sealy Annex, Route 0568
 18 301 University Boulevard
 19 Galveston, Texas 77555
 20
 21
 22 (Roster continued on the next page.)

1 ROSTER (continued):
 2
 3 TEMPORARY VOTING MEMBERS (continued):
 4 N. FRANKLIN ADKINSON, M.D.
 5 Professor of Medicine
 6 Johns Hopkins Asthma and Allergy Center
 7 5501 Hopkins Bayview Circle
 8 Baltimore, Maryland 21224
 9
 10 LESLIE HENDELES, Pharm.D.
 11 Professor of Pharmacy and Pediatrics
 12 University of Florida
 13 1600 S.W. Archer Road, Room PG-05
 14 Gainesville, Florida 32610
 15
 16 MICHAEL SCHATZ, M.D.
 17 Chief, Allergy Department
 18 Southern California Permanente Medical
 19 Group
 20 7060 Claremont Mesa Boulevard
 21 San Diego, California 92111
 22 (Roster continued on the next page.)

1 ROSTER (continued):
 2
 3 TEMPORARY VOTING MEMBERS (continued):
 4 PETER TERRY, M.D.
 5 Professor of Medicine
 6 Johns Hopkins Medical Institutions
 7 Division of Pulmonary and Critical Care
 8 Medicine
 9 1830 E. Monument Street, Suite 500
 10 Baltimore, Maryland 21205
 11
 12 JOHN HOIDAL, M.D.
 13 Professor of Medicine
 14 Chair, Department of Internal Medicine
 15 The Clarence M. and Ruth N. Birrer
 16 Presidential Endowed Chair
 17 30 North 1900 East
 18 4C104 SOM
 19 Salt Lake City, Utah 84132
 20
 21
 22 (Roster continued on the next page.)

1 ROSTER (continued):
 2
 3 FDA PARTICIPANTS (NON-VOTING):
 4 CURTIS ROSEBRAUGH, M.D.
 5 Director, Office of Drug Evaluation II
 6 CDER/FDA
 7
 8 BADRUL CHOWDHURY, M.D., Ph.D.
 9 Director, Division of Pulmonary and
 10 Allergy Drug Products
 11 CDER/FDA
 12
 13 THOMAS PERMUTT, Ph.D.
 14 Director, Division of Biometrics II
 15 CDER/FDA
 16
 17 SALLY SEYMOUR, M.D.
 18 Deputy Director for Safety
 19 Division of Pulmonary and Allergy Drug
 20 Products
 21 CDER/FDA
 22 (Roster continued on the next page.)

1 ROSTER (continued):
 2
 3 FDA PARTICIPANTS (NON-VOTING):
 4 SUSAN LIMB, M.D.
 5 Medical Officer
 6 Division of Pulmonary and Allergy Drug
 7 Products
 8 CDER/FDA
 9
 10 DONGMEI LIU, Ph.D.
 11 Statistical Reviewer
 12 Office of Biostatistics
 13 CDER/FDA
 14
 15
 16
 17
 18
 19
 20
 21
 22

1 A G E N D A
 2
 3 The committee will discuss biologic
 4 license application (BLA) 125277, KALBITOR,
 5 ecallantide injection by Dyax, Corp., for the
 6 treatment of acute attacks of hereditary
 7 angioedema.
 8
 9 8:30 a.m. Call to Order and Introduction of
 10 Committee
 11 William Calhoun, M.D., Acting Chair
 12
 13 Conflict of Interest Statement
 14 Kristine Khuc, Pharm.D., Designated Federal
 15 Official, PADAC
 16
 17 8:45 a.m. Opening Remarks
 18 Badrul Chowdhury, M.D., Director, Division of
 19 Pulmonary and Allergy Products, CDER, FDA
 20
 21 Sponsor Presentation
 22 (Agenda continued on the next page.)

1 AGENDA (continued):
 2
 3 9:00 a.m. Introduction and Overview
 4 William Pullman, M.D., Ph.D., Executive Vice
 5 President of Clinical Development and Medical
 6 Affairs, Dyax Corp.
 7
 8 Clinical Efficacy and Safety
 9 Patrick Horn, M.D., Ph.D., Vice President of
 10 Clinical Development and Medical Affairs,
 11 Dyax Corp.
 12
 13 Safe-Use Conditions
 14 William Pullman, M.D., Ph.D., Executive Vice
 15 President of Clinical Development and Medical
 16 Affairs, Dyax Corp.
 17
 18 Clinical Perspective
 19 Marc Riedl, M.D., M.S., Clinical Immunology and
 20 Allergy, UCLA David Geffen School of Medicine
 21
 22 (Agenda continued on the next page.)

1 AGENDA (continued):
 2
 3 Concluding Remarks
 4 William Pullman, M.D., Ph.D., Executive Vice
 5 President of Clinical Development and Medical
 6 Affairs, Dyax Corp.
 7
 8 10:00 a.m. Questions for clarification
 9
 10 10:15 a.m. Break
 11
 12 FDA Presentation
 13
 14 10:30 a.m. Clinical Overview of the Efficacy of
 15 Ecallantide for the Treatment of Acute Attacks of
 16 Hereditary Angioedema
 17 Susan Limb, M.D., Medical Officer, Division of
 18 Pulmonary and Allergy Products, CDER, FDA
 19
 20
 21
 22 (Agenda continued on the next page.)

1 AGENDA (continued):
 2
 3 Statistical Considerations
 4 Dongmei Liu, Ph.D., Statistical Reviewer,
 5 Office of Biostatistics, CDER, FDA
 6
 7 Clinical Overview of the Safety of Ecallantide for
 8 the Treatment of Acute Attacks of Hereditary
 9 Angioedema
 10 Susan Limb, M.D., Medical Officer, Division of
 11 Pulmonary and Allergy Products, CDER, FDA
 12
 13 11:45 a.m. Questions for clarification
 14
 15 12:00 p.m. Lunch
 16
 17 1:00 p.m. Open Public Hearing
 18
 19 2:00 p.m. Charge and questions to Committee
 20
 21 Committee discussion/vote
 22 (Agenda continued on the next page.)

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 3 3:45 p.m. Break
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 5 4:00 p.m. Committee discussion/vote
 6
 7 5:00 p.m. Adjournment
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1 PROCEEDINGS
2 - - - - -
3 DR. CALHOUN: Good morning. Welcome to
4 the FDA Pulmonary-Allergy Drug Advisory Committee
5 meeting.
6 My name is Bill Calhoun. I'm Professor
7 and Vice Chairman of Medicine at the University of
8 Texas in Galveston. In a minute, we're going to
9 introduce the panel members to you.
10 Just to finish my own introduction, my
11 own personal training is in pulmonary diseases and
12 in allergy and clinical immunology.
13 With that, I'd like to begin by
14 introducing the panel members, having you
15 introduce yourself by name, affiliations,
16 expertise, et cetera, et cetera, and perhaps we'll
17 start with Dr. Hubbard.
18 DR. HUBBARD: My name is Richard Hubbard.
19 I'm a pulmonary physician by training, received my
20 training at Mount Sinai Hospital in New York,
21 spent several years at the NIH. I'm the industry
22 representative for the Pulmonary-Allergy Advisory

1 Committee, and I'm with Pfizer.
2 DR. HOIDAL: My name is John Hoidal. I'm
3 also a pulmonologist at the University of Utah,
4 where I'm professor and chair of the Department of
5 Medicine. My research expertise is in the
6 pathobiochemistry of lung injury.
7 DR. GRUCHALLA: I'm Rebecca Gruchalla.
8 I'm an allergist/immunologist, professor and
9 division chief at UT Southwestern Medical Center
10 in Dallas.
11 DR. TERRY: My name is Peter Terry. I'm
12 Professor of Medicine at Johns Hopkins. My
13 research interests have been in pulmonary
14 physiology and I have a degree in bioethics, also.
15 DR. BORISH: Larry Borish. I'm a
16 professor at the University of Virginia and my
17 research interest is asthma.
18 DR. CARVALHO: I'm Paula Carvalho. I'm a
19 Professor of Medicine at the University of
20 Washington in pulmonary diseases and my research
21 interest is the bronchial circulation.
22 DR. HENDELES: I'm Leslie Hendeles. I'm

1 a clinical pharmacist at the University of Florida
2 in the Pediatric Pulmonary Clinic, and my research
3 interest is the clinical pharmacology of drugs for
4 asthma and allergy.
5 DR. CALHOUN: Dr. Adkinson is not yet
6 here. We'll have him introduce himself when he
7 gets here.
8 DR. KHUC: I'm Kristine Khuc, the
9 designated federal official for this committee.
10 DR. SCHATZ: I'm Michael Schatz. I'm
11 Chief of the Department of Allergy at Kaiser
12 Permanente San Diego and my research interest has
13 been largely asthma as well.
14 DR. BALLOW: Mark Ballow, Women's and
15 Children's Hospital in Buffalo, SUNY Buffalo, and
16 I'm in the Allergy/Immunology Division. My
17 research interest is actually immunology.
18 DR. HONSINGER: I'm Richard Honsinger.
19 I'm a clinical professor at the University of New
20 Mexico. I practice internal medicine, allergy and
21 immunology in Los Alamos, New Mexico.
22 DR. FOGGS: I'm Michael Foggs and I'm

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

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

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

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

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

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

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

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

22 DR. CALHOUN: Okay, thank you. Just some

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

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

9 For topics such as those being discussed
10 at today's meeting, there are often a variety of
11 opinions, some of which are quite strongly held.
12 Our goal is that today's meeting will be a fair
13 and open forum for discussion of these issues and
14 that individuals can express their views without
15 interruption. Thus, as a gentle reminder,
16 individuals will be allowed to speak into the
17 record only if recognized by the chair.

18 We look forward to a productive meeting.

19 In the spirit of the Federal Advisory
20 Committee Act and the Government in the Sunshine
21 Act, we ask that the advisory committee members
22 take care that their conversations about the topic

1 at hand take place in the open forum of this
2 meeting.

3 We are aware that members of the media
4 are anxious to speak with the FDA about these
5 proceedings; however, the FDA will refrain from
6 discussing the details of this meeting with the
7 media until its conclusion.

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

13 Thank you.

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

16 DR. KHUC: The Food and Drug
17 Administration is convening today's meeting of the
18 Pulmonary-Allergy Drug Advisory Committee under
19 the authority of the Federal Advisory Committee
20 Act of 1972.

21 With the exception of the industry
22 representative, all members and temporary voting

1 members of the committee are special government
2 employees or regular federal employees from other
3 agencies and are subject to federal conflict of
4 interest laws and regulations.

5 The following information on the status
6 of this committee's compliance with federal ethics
7 and conflict of interest laws covered by, but not
8 limited to, those found at 18 USC Section 208, and
9 Section 712 of the Federal Food, Drug and Cosmetic
10 Act, are being provided to participants in today's
11 meeting and to the public.

12 FDA has determined that members and
13 temporary voting members of this committee are in
14 compliance with federal ethics and conflict of
15 interest laws.

16 Under 18 USC Section 208, Congress has
17 authorized FDA to grant waivers to special
18 government employees and regular federal employees
19 who have potential financial conflicts when it is
20 determined that the agency's need for a particular
21 individual's services outweighs his or her
22 potential financial conflict of interest.

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

7 Related to the discussions of today's
8 meeting, members and temporary voting members of
9 this committee have been screened for potential
10 financial conflicts of interest of their own, as
11 well as those imputed to them, including those of
12 their spouses or minor children, and, for purposes
13 of 18 USC Section 208, their employers.

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

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

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

5 With respect to FDA's invited industry
6 representative, we would like to disclose that
7 Dr. Richard Hubbard is participating at this
8 meeting as a nonvoting industry representative,
9 acting on behalf of regulated industry.

10 Dr. Hubbard's role at this meeting is represent
11 industry, in general, and not any particular
12 company. Dr. Hubbard is employed by Pfizer.

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

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

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

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

6 Thank you.

7 DR. CALHOUN: Okay. Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 provide recommendation to the agency on this
2 safety issue.

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

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

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

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

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

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

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

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

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

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

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

14 Thank you.

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

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

1 attacks of hereditary angioedema, or HAE.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3 The ecallantide clinical program, which
4 represents a comprehensive approach to the
5 condition, included the development of
6 patient-reported outcome measures, or PROs. An
7 understanding of these measures is critical to
8 understanding the clinical relevance of our Phase
9 3 data.

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

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

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

1 endogenous bradykinin release.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 affect the patients' daily activities.

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

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

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

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

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

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

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

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

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

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

22 EDEMA3, double-blind, was a

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

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

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

18 In the completed studies that enrolled
19 HAE patients, 219 patients received 609 doses of
20 ecallantide and, of these, 25 were aged 10 through
21 17, who were treated for 79 acute episodes.
22 Beyond our BLA, open-labeled continuation trial

1 has treated over 100 patients with over 300 attack
2 treatments.

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

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

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

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

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

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

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

13 EDEMA3 was a Phase 3 randomized,
14 double-blind, placebo-controlled study to evaluate
15 the safety and efficacy of ecallantide versus
16 placebo in patients with acute attacks of HAE.
17 Seventy-two patients were randomized to either a
18 30 milligram subcutaneous dose of ecallantide or
19 to placebo. Data was collected throughout the
20 first four hours and again at 24 hours.

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

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

6 As mentioned earlier, EDEMA3 was a Phase
7 3 randomized, double-blind, placebo-controlled
8 study designed under special protocol assessment
9 agreement with the FDA and designed to evaluate
10 the safety and efficacy of ecallantide versus
11 placebo in patients with acute attacks of HAE.

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

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

22 As you can see, the trial designs are

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 Kaplan-Meier methods were used to look at
13 the time to onset of sustained improvement. And
14 68.6 percent of patients achieved onset of
15 sustained improvement by four hours in the
16 ecallantide group compared to 41.1 percent of
17 placebo patients.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 ecallantide group is better than placebo and the
 2 TOS is statistically significantly better.
 3 Looking at the peripheral attacks, the
 4 decrease in symptom severity and the response to
 5 treatment are better in the ecallantide group than
 6 in the placebo group. Peripheral attacks are
 7 difficult to treat and slow to resolve, so it is
 8 encouraging to see improvement on both measures at
 9 four hours with statistical significance achieved
 10 for TOS.

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

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

22 These observations indicate that

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

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

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

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

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

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

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

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

1 same.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 consistent treatment effect is seen in all
2 populations.

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

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

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

1 groups.

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

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

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

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

1 support from the secondary endpoints and
2 consistency across all studies.

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

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

17 For pediatric patients, the underlying
18 pathophysiology of acute attacks of HAE is the
19 same as in adults; namely, dysregulated plasma
20 kallikrein leading to increased bradykinin
21 production.

22 There is no reason to think that

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

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

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

22 In addition, given the short half-life of

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

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

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

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

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

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

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

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

19 The double-blind population included 100
20 patients treated with ecallantide for a total of
21 125 doses. The HAE patient population of 219
22 patients received a total of 609 doses.

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

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

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

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

1 studies.

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

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

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

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

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

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

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

16 Following medical review of each of these
17 24 cases, Dyax identified 13 as possible
18 hypersensitivity reactions, and these include the
19 four serious adverse events previously noted.

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

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

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

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

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

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

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

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

19 In the Phase 3 studies in which the
20 samples were assayed for neutralizing antibodies,
21 1.6 percent of patients developed neutralizing
22 antibodies to ecallantide in the in vitro assay.

1 numerous therapeutic doses of ecallantide with no
2 further hypersensitivity episodes.

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

9 All patients had a history of allergies.

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

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

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

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

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

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

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

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

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

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

14 DR. PULLMAN: Thank you, Dr. Horn.

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

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

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

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

7 Furthermore, we'll educate patients and
8 their physicians on ecallantide and the
9 identification and treatment of anaphylaxis,
10 including the use of re-challenge procedures.

11 Thus, our overall aim of this plan is to monitor
12 ecallantide use and to ensure that it is used
13 safely, under controlled conditions.

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

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

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

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

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

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

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

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

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

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

22 DR. RIEDL: Mr. Chairman and members of

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 home in excellent condition within four hours.

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

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

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

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

22 Thus, patients regain their normal lives

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

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

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

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

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

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

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

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

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

1 nature of this disease.

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

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

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

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

1 DR. PULLMAN: Thank you, Dr. Riedl.

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

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

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

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

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

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

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

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

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

22 DR. CALHOUN: Okay. Thank you to the

1 patients that were treated in the latter part of
2 EDEMA4?

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

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

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

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

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

21 DR. HORN: The change is very small.

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

1 sponsors for their presentations.

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

4 Dr. Adkinson is here.

5 Frank, could you introduce yourself?

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

11 DR. CALHOUN: Okay. Thank you.

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

14 Dr. Ballow?

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

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

1 was not significant, right?

2 DR. HORN: Right.

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

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

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

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

18 DR. HORN: Same lot of drugs.

19 DR. BALLOW: Okay. Strange.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 DR. CALHOUN: Thank you.

13 Dr. Schatz?

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

19 What was used as the gold standard for
20 the validation?

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

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

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

13 DR. CALHOUN: Dr. Hoidal?

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

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

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

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

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

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

15 DR. CALHOUN: Dr. Hubbard?

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

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

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

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

7 DR. HUBBARD: And was that data captured?

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

11 DR. HUBBARD: Okay.

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

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

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

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

4 DR. CALHOUN: Dr. Honsinger?

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

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

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

22 I would wonder, as you watched your

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

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

12 DR. CALHOUN: Dr. Proschan?

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

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

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

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

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

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

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

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

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

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

9 DR. PROSCHAN: Okay.

10 DR. CALHOUN: Dr. Gruchalla?

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

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

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

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

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

3 DR. HORN: Yes.

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

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

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

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

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

1 think, could be better at this than I can.
 2 But just my question about sensitivity.
 3 Are we missing people that may have potential IgE?
 4 DR. HORN: I'll let Dr. Pullman address
 5 the assay.

6 DR. GRUCHALLA: Okay.

7 DR. PULLMAN: The only thing I can add to
 8 that question is we are having conversations and
 9 dialogue with the agency on that very question,
 10 matrix effects and sensitivity, to ensure that the
 11 assay sensitivities are appropriate.

12 What I can say is the assays went through
 13 a full validation procedure, but we are engaged in
 14 discussions on that topic.

15 DR. GRUCHALLA: Okay.

16 DR. CALHOUN: Dr. Carvalho?

17 DR. CARVALHO: I have two questions.
 18 First of all, was there any objective data
 19 gathered rather than just symptom progression and
 20 the patients' grading scales? Were there any
 21 hemodynamic parameters obtained or flow volume
 22 loops, actual edema measurements during the study?

1 DR. CALHOUN: Dr. Hendeles?

2 DR. HENDELES: I have a few questions.
 3 One relates to the risk of a Type I statistical
 4 error. It seems like the same data got analyzed
 5 several times in several different ways and I'm
 6 just wondering whether you took into account that
 7 and made adjustments for it in the statistical
 8 analysis.

9 The second question is, are there any
 10 excipients in the formulation other than the
 11 active drug that could account for the allergic
 12 reaction.

13 The third question -- would you like me
 14 to stop and you answer it?

15 DR. PULLMAN: That might be best. Thank
 16 you. I got the first two, I believe.

17 DR. HENDELES: Okay, go ahead.

18 DR. PULLMAN: So risk of Type I errors in
 19 the analyses. There were no multiple adjustments
 20 necessary in the E4 or the E3 settings for the
 21 primary endpoints, so none were applied.

22 But in the integrated dataset, to ensure

1 DR. PULLMAN: No, there were not. But we
 2 did measure blood pressure over the course of the
 3 attack episode and it shows what you might expect.
 4 There's some relative hypertension in both placebo
 5 and ecallantide groups and no significant
 6 difference between the two.

7 But we did not employ any other form of
 8 pharmacodynamic marker in the EDEMA3/EDEMA4
 9 program with respect to kallikrein, C4 levels, et
 10 cetera.

11 DR. CARVALHO: And I have a second
 12 question, if I may. I'm curious.

13 Looking at the data, was there any site
 14 change with repeated treatments? In other words,
 15 were people more likely to have laryngeal symptoms
 16 later, abdominal symptoms later, peripheral, as
 17 patients were treated over time?

18 DR. PULLMAN: There was no pattern, as we
 19 expect, unpredictable and wide variety of attack
 20 locations presented, so no consistent systematic
 21 pattern for any particular patient or population.

22 DR. CARVALHO: Thank you.

1 independency, we only counted patients on their
 2 first exposure, which is why, if there were 168
 3 patients between the two, the 143 is presented.
 4 So we've only counted them on one occasion, so
 5 that we've reduced that chance of lack of
 6 independence.

7 With respect to excipients, there is host
 8 cell protein in the drug substance and drug
 9 product. The host cell protein is actually at a
 10 low level. It's at eight parts per million, which
 11 is below the most stringent threshold of 10.

12 In the early part of the process, which
 13 actually applied to EDEMA0, 1 and 2, this was the
 14 clinical trial material supplied for intravenous,
 15 levels of host cell proteins were higher, about
 16 70-fold higher.

17 Based on that, we actually introduced an
 18 additional step in the manufacturing process, an
 19 anion exchange step, reduced it 70-fold, brought
 20 it well within industry accepted acceptance
 21 criteria for host cell protein. But that is the
 22 one that is there.

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

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

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

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

22 We've given the epinephrine, for example

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

6 DR. CALHOUN: Dr. Foggs?

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

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

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

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

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

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

16 DR. CALHOUN: Dr. Borish?

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

21 DR. CALHOUN: Sorry. Yes.

22 DR. HORN: So could you just clarify the

1 question for me, please?

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

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

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

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

22 DR. FOGGS: I understand that, but still,

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

3 DR. HORN: Okay.

4 DR. CALHOUN: Now, Dr. Borish?

5 DR. BORISH: Thank you.

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

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

20 The second question is in regard to the
21 30 milligram dose. I saw lots of PK data, but I'm
22 curious whether you know that at that 30 milligram

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

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

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

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

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

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

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

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

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

16 Slide up, please.

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

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

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

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

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

11 DR. HORN: No.

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

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

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

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

4 At this point, we're going to take a
5 13-minute break. It's 10:17 by my watch. We will
6 convene promptly at 10:30.

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

11 (A recess was taken.)

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

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

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

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

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

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

1 variable between individuals and within an
2 individual.

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

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

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

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

22 Since angioedema is common to both HAE

1 and anaphylaxis, epinephrine is occasionally used
2 for its vasoconstrictive properties in acute HAE
3 attacks, but epinephrine's efficacy for acute
4 attacks is limited.

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

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

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

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

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

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

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

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

22 Ecallantide is a new molecular entity and

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

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

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

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

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

1 studies will be presented separately in the next
2 slide.

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

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

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

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

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

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

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

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

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

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

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

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

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

4 If no improvement was noted within four
5 hours, a second dose, dose B, could be
6 administered. Patients could receive a maximum of
7 20 doses for separate attacks.

8 Escalating intravenous doses from five to
9 20 milligrams per meter squared and a 30 milligram
10 subcutaneous dose were given in sequential dose
11 cohorts.

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

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

1 2 studies.

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

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

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

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

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

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

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

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

1 During the open-label phase of both
2 studies, patients presenting with new HAE attacks
3 received ecallantide 30 milligrams subcutaneously.

4 New patients who had not participated in the
5 double-blind phase were also eligible to enroll.

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

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

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

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

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

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

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

1 the statistical analysis.

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

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

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

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

1 about the impact of these imputations.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 As shown here, this is the same severity

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

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

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

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

22 To get a sense of the proportion of

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

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

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

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

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

1 there are 143 unique patients.

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

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

13 A total of 15 patients under the age of
14 18 years have been treated with the to-be-marketed
15 30 milligram subcutaneous dose. Whether this
16 number is sufficient to draw conclusions about the
17 efficacy and safety of ecallantide in the
18 pediatric population will be a topic for
19 discussion later today.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 When comparing the patients enrolled

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

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

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

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

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

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

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

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

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

1 amendment who clearly performed worse.
 2 This table summarizes the characteristics
 3 of those six placebo outliers. Both male and
 4 female patients were represented and the age was
 5 close to the mean age for the total population.
 6 The patients were each recruited at a different
 7 U.S. study site.
 8 No single anatomic attack site
 9 predominated. All of the patients required a dose
 10 B for persistence or worsening of symptoms. Some
 11 patients appeared to improve after administration
 12 of dose B, while one patient reported no
 13 improvement and the second worsened considerably,
 14 requiring hospitalization for a worsening GI
 15 attack.
 16 Based on this look at the individual
 17 outliers, there are no clear characteristics that
 18 distinguish these six patients from the rest of
 19 the study population.
 20 Now, all of the data that I have shown
 21 you so far was based on single dose data from the
 22 controlled phase of the EDEMA3 and EDEMA4. Before

1 comparison.
 2 Numerically, the TOS and MSCS values
 3 suggest that there is no apparent decline in
 4 efficacy over repeat dosing. However, keep in
 5 mind that the later values are based on fewer and
 6 fewer patients.
 7 Given that the open-label phase lasted
 8 almost two years, one might have expected a larger
 9 number of patients presenting for repeat dosing.
 10 The patient numbers may reflect the inherent
 11 variability of the disease or may be a byproduct
 12 of study logistics.
 13 Alternatively, there may have been some
 14 self-selection among patients who were responders
 15 versus those who were non-responders. In other
 16 words, patients who experienced a benefit from
 17 ecallantide may have continued to present for
 18 subsequent attacks, while patients with lesser
 19 responses may have chosen not to participate any
 20 further.
 21 In summary, the limitations of the EDEMA3
 22 data and the questionable robustness of the EDEMA4

1 I conclude this overview of the efficacy results,
 2 I will briefly discuss repeat use data. As
 3 mentioned earlier, data to support the efficacy of
 4 repeat dosing comes primarily from the open-label
 5 portion of EDEMA3.
 6 This table summarizes the patient
 7 exposure during the EDEMA3 open-label study, which
 8 lasted nearly two years in duration. In addition
 9 to patients rolling over from the double-blind
 10 phase, 18 new patients were enrolled and treated.
 11 A total of 160 attacks in 66 patients were
 12 included.
 13 As you can see, the majority of patients
 14 were treated for one additional attack during the
 15 open-label study. One patient was treated for 13
 16 attacks.
 17 This table summarizes the main efficacy
 18 findings for the repeat dosing open-label phase of
 19 EDEMA3 up through the sixth treatment episode.
 20 The first row of the table shows the mean TOS and
 21 MSCS results reported for the ecallantide arm
 22 during the double-blind portion of the study for

1 results have been the primary issues for the
 2 agency's efficacy review of ecallantide. These
 3 results will be the focus of the discussion later
 4 this afternoon. In addition, as mentioned
 5 earlier, the pediatric data is limited and will be
 6 another issue for discussion.
 7 With these issues highlighted, I will now
 8 turn it over to Dr. Liu, who will present a
 9 detailed look at the statistical analysis of
 10 efficacy.
 11 DR. LIU: I'm Dongmei Liu, the
 12 statistical reviewer, and I will be presenting the
 13 efficacy result of this application.
 14 The discussion on efficacy is split into
 15 three major parts; collective evidence on efficacy
 16 in the two Phase 3 studies, sensitivity analysis
 17 on data imputation, and then we will have some
 18 information on pediatric patients.
 19 Before we get into a detailed discussion,
 20 I'd like to make one point clear at the beginning.
 21 In efficacy analysis, there are various ways to
 22 analyze data. Some of the analysis we did here

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

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

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

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

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

1 were the ones who performed poorer.

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

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

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

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

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

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

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

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

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

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

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

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

16 The treatment difference measured by a
17 change of MSCS is negative .09 in the original 52
18 patients, with a P value of .8, and it is negative
19 .9 in the additional 44 patients recruited after
20 sample size increment, with a P value less than
21 .001. The treatment difference was increased
22 10-fold.

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

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

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

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

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

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

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

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

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

22 The known hypothesis of the test is that

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 That closes our discussion on collective

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

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

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

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

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

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

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

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

1 had emergent symptoms.

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

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

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

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

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

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

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

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

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

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

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

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

22 This slide represents the P value of

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

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

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

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

22 So we call it anticonservative imputation

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

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

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

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

22 As we already talked in the previous

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

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

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

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

22 Because the sponsor proposed ecallantide

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

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

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

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

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

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

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

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

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

22 The safety database for ecallantide is

1 based primarily on the HAE studies, which included
2 219 unique HAE patients. A total of 609 doses
3 were administered. As shown in this table,
4 approximately half of the patients received one
5 dose.

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

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

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

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

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

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

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

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

1 particular adverse events in more detail.

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

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

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

1 frequently in the ecallantide group.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 doses administered.

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

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

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

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

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

1 minute of completing her sixth intravenous
 2 infusion.

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

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

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

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

1 dosing.

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

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

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

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

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

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

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

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

22 Finally, patient D from EDEMA1

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

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

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

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

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

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

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

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

22 Six of the nine patients successfully

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

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

10 However, we do not interpret the negative
11 re-challenges to mean that the original reactions
12 were not true hypersensitivity reactions.

13 Negative re-challenges may be due to a loss of
14 sensitization over time or the absence of certain
15 co-factors that were present during the original
16 reaction.

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

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

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

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

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

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

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

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

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

22 There were few patients treated for more

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

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

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

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

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

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

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

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

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

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

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

14 Thank you.

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

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

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

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

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

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

1 and not debate those two interpretations.

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

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

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

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

13 DR. CALHOUN: Please.

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

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

1 called in and got two vial assignments.

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

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

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

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

22 If one were to ask that question with a

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

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

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

14 DR. CALHOUN: Maybe I can simplify the
15 question.

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

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

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

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

10 DR. CALHOUN: Okay. Dr. Schatz?

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

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

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

3 DR. CALHOUN: Mr. Proschan?

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

8 Maybe it's not that one. The one that
9 had two dotted lines. Slide 4. Okay. That just
10 has one.

11 Yes. So the 52, is that the number to
12 the left of the rightmost line or the number to
13 the left of the leftmost line?

14 DR. LIU: That's the number to the left
15 of the line. So the number of patients to the
16 left of the black dotted line are the predefined
17 52 patients and the dots in the right-hand side of
18 the black dotted line are the additional 44
19 patients.

20 DR. PROSCHAN: Okay. I have to point out
21 that I'm not very good at discerning the
22 difference between those two colors. So is the

1 black one the right one?
 2 DR. LIU: Yes, yes. Sorry.
 3 DR. PROSCHAN: The right side. Okay.
 4 So why do you have those two lines? I
 5 mean, why do you have -- after you changed the
 6 protocol -- but if those originally -- if you were
 7 planning to go to 52 anyway, why even look at that
 8 leftmost line, unless you think that somehow as
 9 soon as they changed the protocol, they started
 10 thinking differently or something?
 11 DR. LIU: That's a good question. We
 12 actually had analysis results available for the
 13 separation based on the blue dotted line, but we
 14 didn't present it here. It's not substantially
 15 different from splitting the population based on
 16 the black dotted line, so the conclusion wouldn't
 17 change.
 18 DR. CALHOUN: Dr. Gruchalla?
 19 DR. GRUCHALLA: Yes. I believe,
 20 Dr. Limb, you were saying that the presence of IgE
 21 was not predictive. The question I have is was
 22 it -- so maybe seroconversion alone is not what's

1 IgE, drug-specific IgE, looked at before and then
 2 after the drug was given, because I don't know if
 3 there's -- could this drug be cross-reactive to
 4 something else, say, penicillin, which I know
 5 that's not the case. But could they have
 6 preexisting IgE antibodies?
 7 DR. LIMB: So no IgE was detected at
 8 baseline against the drug product. I believe it
 9 was not until the fourth treatment episode that
 10 IgE was detected.
 11 DR. ADKINSON: Dr. Limb, I didn't hear
 12 this in your presentation, but in the agency's
 13 briefing document, you raised a concern, which I
 14 share, that in theory, antibodies directed against
 15 the product might have an adverse perturbation of
 16 the intrinsic clotting system and lead to some
 17 state of hypercoagulability if they persist over
 18 time.
 19 Has data been provide with regard to that
 20 potential possibility in any of these studies?
 21 Has the sponsor addressed this in any way?
 22 DR. LIMB: I believe the company is in

1 important, also, but the quantity of IgE.
 2 Were titers of IgE able to be analyzed in
 3 the study? That's the first question.
 4 The second one is were IgE antibodies to
 5 the drug looked at before and then after drug
 6 treatment? Because the other question I have is,
 7 is there any kind of cross-reactivity between that
 8 agent and any other type of drug? So basically,
 9 those are the two questions.
 10 DR. LIMB: Yes, IgE titers were taken.
 11 But based on those titers and the hypersensitivity
 12 reactions we identified, there wasn't any clear
 13 correlation, and the patient who appeared to have
 14 the most severe reaction, with anaphylaxis two
 15 times, her titers in particular were
 16 intermittently positive and negative.
 17 And that may get back to the original
 18 issue we've had with looking at the assays, that
 19 there may be sensitivity issues.
 20 I'm sorry. And then your second
 21 question?
 22 DR. GRUCHALLA: The second question, was

1 the process of conducting in vitro
 2 cross-reactivity studies to look at that question.
 3 In terms of the clinical data, we didn't see any
 4 evidence of increased thrombotic events in the
 5 adverse events.
 6 DR. ADKINSON: That would be a pretty
 7 crude, though, outcome.
 8 DR. LIMB: That's true.
 9 DR. ADKINSON: So no coagulation studies
 10 were done as part of these clinical trials, the
 11 pivotal clinical trials?
 12 DR. LIMB: Coagulation parameters were
 13 studied serially, assessed serially, because we
 14 were actually concerned about a prolongation in
 15 the PTG based on animal -- I'm sorry -- in vitro
 16 studies.
 17 And there was some slight prolongation of
 18 APTG that was seen, but it wasn't clinically
 19 significant. And then as far as the converse
 20 situation with hypercoagulability, we didn't see
 21 any events to suggest that was the case.
 22 DR. CALHOUN: Dr. Hendeles?

1 DR. HENDELES: Dr. Liu, could you please
2 address my earlier question about the multiple
3 statistical analysis, for example, in the
4 comparison of the first -- in EDEMA4, in a
5 comparison of the first 52 versus 44?

6 That data was analyzed at least twice,
7 the first time, the whole group, and then the
8 subgroups, and then you've repeated the analysis,
9 and then there were the other analyses. And I'm
10 just wondering whether there is an increased risk
11 of a Type I error.

12 DR. LIU: These analyses are actually
13 independent. So either you analyze the data based
14 on the whole population or you analyze data based
15 on the study period. So because they're
16 independent, there is no correction on the Type I
17 error.

18 DR. HENDELES: Maybe my biostatistics
19 professor was wrong, but I was taught that if you
20 keep on doing tests, that you have to make some
21 kind of adjustment, because eventually -- I mean,
22 you have at least a five percent chance of finding

1 a difference when no difference exists, and the
2 more tests you do, the more likely you're going to
3 find a difference.

4 DR. LIU: That is correct, but it's based
5 on you do sequential tests. So this is actually
6 based on independent look at the data in two
7 different ways. It's not the same set of data
8 tested by two different kind of hypotheses.

9 DR. PERMUTT: I think what Dr. Liu says
10 is true about any given single analysis. I think
11 your point is well taken that there are a lot of
12 different things that we're looking at here and
13 the probability for any one of them to go wrong is
14 quite a bit more than the nominal probability of
15 error in a single test.

16 In particular, the usual way of dealing
17 with that in the FDA's work is to carefully
18 pre-specify the primary analysis.

19 And it's worth noting that what you got
20 from the sponsor is not the carefully
21 pre-specified primary analysis of the individual
22 studies, but a pooled analysis that was decided on

1 post hoc and it makes the overall data look rather
2 better than the separate analyses of the
3 individual studies.

4 DR. CALHOUN: Dr. Borish?

5 DR. BORISH: Yes. Could someone put up
6 Dr. Limb's slide 22?

7 Part of the concerns raised about this --
8 Dr. Limb, slide 22 -- were the differences in the
9 performance of the initial enrolled subjects
10 versus after the sample size was increased. And
11 when I look at the comparison in slide 22 of the
12 difference in this group, there's a number that
13 really jumps out at you that these patients are
14 quite different.

15 The only objective data we have as to the
16 severity of the patient's disease is their
17 functional C1 inhibitor concentrations, and in the
18 second half of the study, those numbers
19 substantially drop.

20 Now, this being an autosomal -- now, the
21 functional, of course, reflects -- so I'm
22 referring to the line there where it says "mean

1 percent lower" -- lowest functional C1 inhibitor,
2 left-hand side, 30.29, much, much lower on the
3 right-hand side. So those are the only objective
4 data we have as to these patients' disease.

5 As an autosomal dominant -- that number,
6 first of all, is a function both of how much
7 protein they have and whether that protein works
8 or not. So it's an amalgam of both of those
9 statistics. I don't know how much C1 inhibitor it
10 takes to inhibit C1. I don't know how much it
11 takes to inhibit kallikrein. But clearly, the
12 later patients can't do either very well.

13 Now, I suspect when they went to the
14 second half, I think we heard this, the company
15 had to expand the number of sites, given the
16 rarity of this disease and it's an orphan disease.
17 And knowing the ways of the world, I suspect that
18 when they expanded the number of sites, they did
19 exactly what I would predict.

20 Sites who were, for lack of a better
21 word, desperate or who had desperate patients who
22 were doing extremely poorly were the ones that

1 were rushed to enroll in the study and rushed to
 2 enroll those specific patients in the study.
 3 And I think it's the patients who have
 4 much worse disease objectively by these numbers
 5 who are clearly going to be the responders or, to
 6 put it another way, when you only have 13 percent
 7 functional C1 inhibitor, then when you're in the
 8 placebo group, you are going to get worse.
 9 I don't think those six patients are
 10 outliers. I think those six patients did poorly
 11 because that's what you do when you have 13
 12 percent C1 inhibitor, whereas when you have 30
 13 percent C1 inhibitor, maybe you do okay or hold
 14 your own.
 15 But I would love to see a data analysis
 16 looking at how people did based on what their
 17 functional C1 inhibitor levels were. But there's
 18 a big difference between the two halves of this
 19 and I think it's probably because worse patients
 20 from different worse sites came in later.
 21 DR. HENDELES: But those placebo groups
 22 did better in that second half.

1 DR. LIMB: The collection of serum
 2 tryptase was not systematic. The data that I gave
 3 you are what data were available. So the patients
 4 that I didn't present a serum tryptase level for
 5 were because there was no serum tryptase level to
 6 report.
 7 In terms of the -- I'm sorry. And then
 8 you had a second question.
 9 DR. FOGGS: Well, that essentially
 10 answers the second question as well.
 11 My concern was that there was lack of
 12 protocol for post-systemic anaphylaxis assessment
 13 with regards to a test that has significant
 14 utility in delineating whether or not the patients
 15 had systemic anaphylaxis, realizing that the
 16 patients who had normal serum tryptase levels
 17 could still have had systemic anaphylaxis, which
 18 is why I recommended the mature tryptase level. I
 19 think that should part of a protocol.
 20 DR. LIMB: I will add that, at least in
 21 the patient who had severe anaphylaxis in EDEMA3,
 22 there was an attempt to obtain serum tryptase, but

1 DR. BORISH: No, no. The six outliers
 2 were -- that the six patients got worse in that
 3 second half of the study, whereas in the first
 4 half of the study, the placebo patients held their
 5 own.
 6 DR. CALHOUN: Dr. Foggs?
 7 DR. FOGGS: Concerning systemic
 8 anaphylaxis, I notice that the serum tryptase
 9 level was checked, but it seems as though some of
 10 the patients had that particular test excluded.
 11 Was there a specific reason for that lack
 12 of uniformity in terms of post-anaphylaxis
 13 assessment?
 14 In addition, that's a corollary to the
 15 re-challenge phenomena, because the matured
 16 tryptase has greater sensitivity and what was
 17 reported in the data was the total serum tryptase.
 18 The second question is, is there any
 19 reason that the mature tryptase was not utilized
 20 instead of the total serum tryptase to increase
 21 sensitivity with regards to likelihood of
 22 recognizing activation of tissue mass cells?

1 they couldn't establish IV access. So I think
 2 individual investigators may have attempted to
 3 obtain that information, but it wasn't included in
 4 the protocol.
 5 DR. CALHOUN: Dr. Hubbard?
 6 DR. HUBBARD: Yes. I have a question. I
 7 think it's for the sponsor. But I've noticed
 8 something in the tables provided by the agency and
 9 that has to do with the schedule of procedures in
 10 EDEMA3 and in EDEMA4.
 11 And I guess it leads me to question
 12 exactly how was the study done, because in EDEMA3,
 13 I see that the symptom complex assessment and the
 14 severity assessments were done by a phone call.
 15 Does that mean the patients were
 16 ambulatory and had gone home? And then in EDEMA4,
 17 I see that it was done via e-diary.
 18 So it looks like the assessments were
 19 done different ways for each study, so I don't
 20 know how comparable they are, because if you have
 21 patient-reported outcomes, they usually have to be
 22 done the same way. And I wondered whether the

1 patients were actually in clinic during all their
2 evaluation or were they ambulatory?

3 DR. HORN: In both of the Phase 3
4 studies, the endpoints and the time points
5 collected for the PRO were captured in the
6 electronic diary and they were entered directly
7 into the electronic diary at all time points.

8 The patients went to an investigator
9 site. They were dosed with study medication.
10 They remained in that investigator's site for the
11 first four hours or to collection of the primary
12 endpoint.

13 After that point, they were sent home and
14 at 24 hours, the diary went off and rang a bell.
15 They got a call from the site at 24 hours
16 reminding them to do the electronic diary, and
17 they completed the electronic diary.

18 When they came in for the seven-day
19 follow-up period, they brought the electronic
20 diary with them. All that data was then
21 transferred to the database from the electronic
22 diary. But all data related to PRO was captured

1 directly into the electronic diary.

2 DR. CALHOUN: Dr. Honsinger?

3 DR. HONSINGER: Certainly, in other drugs
4 we -- in other drug allergies, we've not been able
5 to identify IgG or IgE antibodies many times. It
6 many times is not the drug; it's some metabolite
7 of the drug. And so I think that this lack of
8 correlation between the specific IgE and the IgG
9 data doesn't necessarily mean that this is not an
10 allergy reaction.

11 In addition, we certainly saw evidence of
12 several anaphylaxis cases that looked like a very
13 definite anaphylaxis. But I wonder how many other
14 anaphylaxis cases we might have seen if these
15 patients had not been treated.

16 So I presume and would ask did patients
17 receive treatment, that is, patients that came in,
18 they were treated. They were also getting
19 standard treatment, which may not work, but it
20 includes H1 and H2 antihistamines, includes
21 epinephrine, includes steroids. These things may
22 not stop angioedema, but they may stop

1 anaphylaxis.

2 DR. CALHOUN: Is there a response?
3 That's an important point.

4 Dr. Ballow?

5 DR. BALLOW: I also want to follow-up on
6 these hypersensitivity reactions. We've heard
7 some information that the testing -- I guess it's
8 RAST testing, IgE specific. It doesn't really
9 correlate in many of these patients.

10 And then there was some reference, I
11 think, in the documentation that there was also
12 IgG antibodies, but we didn't hear very much data
13 on that part of the in vitro testing.

14 We didn't hear anything about what the
15 mode is or the molecule to which either the IgE or
16 the IgG antibody specificity is directed against.
17 We know it's made in yeast. And there was one
18 comment that there were IgG antibodies in some
19 yeast component.

20 So there's a lot of information that in
21 order to try to figure out what the scope of these
22 hypersensitivity reactions are, we don't have

1 enough information. Now, maybe that's one of the
2 questions that the FDA is asking in their first
3 question.

4 But is there any data, more data
5 available about what part of the molecule it's
6 directed? Is it directed against the yeast? Is
7 it directed against the glycosylation point, as
8 we've seen with some of the monoclonal antibodies
9 at Dr. Borish's institute, with cetuximab? We
10 need more information to try to understand more
11 about these hypersensitivity reactions.

12 DR. LIMB: I think you've raised several
13 good points and, certainly, I think our first
14 question goes into some of that.

15 As far as the IgE antibodies go, I don't
16 have additional information aside from what's
17 already been provided in the briefing package
18 regarding what specific moiety might be involved,
19 and I think a lot of that still has to be worked
20 out.

21 So really what we're basing our safety
22 assessment on is on what we've seen clinically,

1 and that is that there are cases of anaphylaxis
2 and that it occurs at a rate greater than two
3 percent, maybe somewhere as high as four percent
4 or even higher, if there are cases that are going
5 undiagnosed.

6 DR. CALHOUN: Finally, for this morning,
7 Dr. Hoidal.

8 DR. HOIDAL: Just a couple questions for
9 Dr. Liu.

10 In the responder analysis that you
11 presented, was that in the intention to treat as
12 treated or in the intention to treat as
13 randomized?

14 DR. LIU: As treated, intention as
15 treated.

16 DR. HOIDAL: Okay. And then if one looks
17 as these two indices, the TOS and the MSCS, do
18 they distinguish themselves in any way in the
19 robustness of response?

20 DR. LIU: I think the sponsor did some
21 analysis about the correlation between the two
22 efficacy endpoints, the correlation between TOS

1 and MSCS. Probably they have slides to show that.

2 Is that your question?

3 So this is based on the BLA submission.

4 The sponsor did analysis on correlation between
5 TOS and MSCS and there are not great correlations
6 between the two efficacy endpoints. We don't have
7 a slide to show that. That's the conclusion.

8 DR. CALHOUN: Okay. Thank you.

9 Again, for the sake of time, we're going
10 to end discussion this morning. We will take a
11 52-minute lunch break. We're going to reconvene
12 at 1:00 p.m. promptly. There will be time -- I
13 know Dr. Adkinson has a question. There will be
14 time following the lunch break and the open public
15 hearing portion of the meeting for brisk and
16 detailed discussion.

17 So thank you very much.

18 (Whereupon, at 12:05 p.m., a lunch recess
19 was taken.)
20
21
22

1 AFTERNOON SESSION

2 DR. CALHOUN: Good afternoon, folks. The
3 next item on the agenda this afternoon is the open
4 public hearing.

5 The open public hearing, we have six
6 speakers from the public. I'll announce them
7 individually. They will have four minutes for
8 their presentation. If there are questions
9 specifically related to that presentation from the
10 committee, we can take those at that time. We'll
11 have the time to do that.

12 So this is the statement for the
13 beginning of the open public hearing.

14 Both the Food and Drug Administration and
15 the public believe it is a transparent process for
16 information-gathering and decision-making. To
17 ensure such transparency at the open public
18 hearing section of the advisory committee, FDA
19 believes that it is important to understand the
20 context of an individual's presentation.

21 For this reason, the FDA encourages you,
22 the open public hearing speaker, at the beginning

1 of your written or oral statement, to advise the
2 committee of any financial relationships that you
3 may have with the sponsor, its product and, if
4 known, its direct competitors.

5 For example, this financial information
6 may include the sponsor's payment of your travel,
7 lodging or other expenses in connection with your
8 attendance at this meeting.

9 Likewise, the FDA encourages you, at the
10 beginning of your statement, to advise the
11 committee if you do not have such financial
12 relationships. If you choose not to address this
13 issue of financial relationships at the beginning
14 of your statement, it will not preclude you from
15 speaking.

16 The FDA and this committee place great
17 importance in the open public hearing process.
18 The insights and comments provided can help the
19 agency and this committee in their consideration
20 of the issues before them.

21 That said, in many instances and for many
22 topics, there will be a variety of opinions. One

1 of our goals today is for this open public hearing
2 to be conducted in a fair and open way, where
3 every participant is listened to carefully and
4 treated with dignity, courtesy and respect.
5 Therefore, please speak only when recognized by
6 the chair. Thank you for your consideration.

7 So, again, before we start, five of our
8 presenters are from the United States Hereditary
9 Angioedema Association and they will be
10 representing themselves.

11 The first of our speakers is Sally
12 Urbaniak.

13 MS. URBANIAK: Good afternoon. My name
14 is Sally Urbaniak. I live in Jacksonville,
15 Florida. I very much appreciate having the
16 opportunity to address the committee and the FDA
17 staff.

18 The HAE Association paid for my travel
19 here today and I have no financial ties to Dyax,
20 other than a small number of shares that I have
21 purchased as a symbolic gesture of my vigorous
22 support for HAE research.

1 you wonder if you will even make it to the
2 bathroom before passing out.

3 You want to ignore the dangers of not
4 seeking medical help for what you know is going to
5 be a miserable attack. You want to just stay home
6 and tough it out. But then the next wave of
7 excruciating pain hits and your spouse intervenes
8 and convinces you to make another trip to the ER
9 for fluids and pain medicine.

10 You are so weak. You can barely muster
11 the strength to call in sick at work, but you have
12 to. And when you do, you can sense your boss'
13 frustration by the tone of his voice, because this
14 is the second time you've called out sick in the
15 past week and a half.

16 On your way to the hospital, you start
17 thinking of how you're going to handle the ER
18 staff's not so subtle questions that all but
19 directly accuse you of being a drug seeker. You
20 feel so weak and sick at this point, but you know
21 those endless questions are coming.

22 Before you even arrive at the hospital,

1 I want to take a slightly different
2 approach during my time with you this afternoon.
3 Let me start by asking each of you to step out of
4 your roles as medical professionals and, for the
5 next couple of minutes, think of me as your sister
6 or your daughter. Please spend a few moments with
7 me living the life of a severely affected HAE
8 patient.

9 Imagine waking up one morning and as you
10 get out of bed, you realize your feet are so
11 swollen that even a short walk to the shower is
12 going to be painful.

13 When you stand up, your feet feel like
14 they are ready to explode from supporting your
15 body weight. But soon you have no choice rather
16 than to get moving, because a sharp, gnawing pain
17 in your stomach signals a sickening and urgent
18 need to throw up.

19 The fluids which cause the swelling have
20 leaked out of your circulatory system and your
21 blood pressure is very low. The lightheaded,
22 faint feeling that you're experiencing, it makes

1 your swallowing becomes more difficult and it
2 feels like your throat is swelling. You're
3 somewhat content that the car is just dark enough
4 so your spouse doesn't notice how frightened you
5 are that your throat is closing.

6 When you arrive at the ER, you say a
7 silent prayer that you will not have to spend the
8 next 72 hours looking at the glistening reflection
9 of the surgical knives that the doctors have
10 placed near your bed so they can swiftly cut a
11 hole into your windpipe to prevent suffocation
12 from a compromised airway.

13 Ladies and gentlemen, the pain, fear and
14 emotion or emotional burden borne by me and
15 thousands of other HAE patients is inordinately
16 tragic because it's preventable. Clinical data
17 shows that ecallantide is an effective
18 (inaudible).

19 DR. CALHOUN: Thank you. Our next
20 speaker is Jenny Barnes.

21 MS. BARNES: Good afternoon. My name is
22 Jenny Barnes. I do not have any financial ties to

1 Dyax. I am not a shareholder. And the HAE
 2 Association paid for my travel here today.
 3 I am appearing before you today, ladies
 4 and gentlemen, not as a patient, but as the mother
 5 of a severely affected young man with HAE.
 6 My son, Jim, began suffering from severe
 7 abdominal attacks at the age of five. I can
 8 vividly recall the horror of having watched him
 9 suffer until the only medicine we could find at
 10 our disposal was Demerol that would mercifully put
 11 him to sleep.
 12 In his subsequent years, Jim bravely
 13 endured frequent disabling swelling and pain. The
 14 relentless onslaught of HAE attacks resulted in an
 15 inordinate number of missed school days and
 16 prevented him from the day-to-day activities
 17 enjoyed by boys his age.
 18 As if the pain -- I'm sorry. As if the
 19 pain and disability haunting Jim wasn't enough, he
 20 had his first laryngeal swelling attack at age 12.
 21 This dangerous life-threatening event required
 22 intubation in ICU that lasted three days.

1 to society.
 2 I won't know what kind of man Jim was
 3 going to become, because on June the 6th, 2008, he
 4 had a laryngeal attack and he went to the
 5 emergency room where he later died. The autopsy
 6 labeled asphyxiation due to laryngeal edema.
 7 I am here addressing you today because
 8 Jim's death and the passing of at least three
 9 other patients who suffocated from acute HAE
 10 attacks over the past 18 months were totally
 11 preventable.
 12 Ecallantide, the product before you
 13 today, has been shown to be an effective therapy
 14 for stopping throat swelling swiftly. Clearly, if
 15 available, this medicine would have saved my
 16 precious son's life.
 17 I stand before you heartbroken, but
 18 resolute in desire to do whatever I can to prevent
 19 another mother from the unspeakable grief that
 20 accompanies losing a child to HAE.
 21 I will never have the privilege of
 22 celebrating my son's achievements, helping him

1 The episode of laryngeal swelling
 2 provided tangible evidence that Jim's HAE was
 3 worsening, and at that point, we had no choice
 4 other than start him on an anabolic steroid.
 5 While these medicines are contraindicated
 6 in 12-year-old boys, we concluded that the risk of
 7 death from asphyxiation outweighed those
 8 associated with androgen therapy in a prepubescent
 9 youngster.
 10 The years of emotional trauma wrought by
 11 pain, the looming threat of death by suffocation,
 12 and anabolic steroid therapy took its toll on Jim.
 13 When he was 15, Jim suffered an emotional meltdown
 14 that was clearly steroid-related. The steroid
 15 rage that Jim exhibited landed him in protective
 16 custody setting.
 17 In the past two years, Jim began to show
 18 a glimmer of promise, thanks to intensive therapy
 19 and the fact that his growth into a man diminished
 20 some of the steroid effects. By age 19, he had a
 21 job and we finally began to see the makings of a
 22 young man that was proving himself to be an asset

1 through life's inevitable bumps, or experiencing
 2 the joys of attending his wedding, holding my
 3 grandchildren, celebrating his successes, and
 4 share in his life's milestones.
 5 You have the power today to approve
 6 ecallantide and, in doing so, ensure that no other
 7 HAE mother ever shares a story like mine. He did
 8 not have to die, suffocating this way, and he
 9 suffocated and it's not acceptable.
 10 I respect you and I thank you for your
 11 time.
 12 DR. CALHOUN: Thank you.
 13 The next speaker is Dr. Henry Li.
 14 DR. LI: Good afternoon. A financial
 15 disclosure, I was a PI and a consultant for Dyax
 16 as well as the four other companies who are
 17 involved in the HAE treatment development.
 18 HAE Association invited me to speak here
 19 on behalf of the community of physicians as well
 20 as HAE patients, but nobody pays me to be here. I
 21 do not own any stock in any of the companies.
 22 I'm a practicing allergist and I also

1 hold academic appointment in Georgetown University
2 Medical Center as well as the Johns Hopkins
3 Asthma-Allergy Center.

4 I am here today to provide the committee
5 and the FDA staff the viewpoint of a physician who
6 is taking care of more than 50 HAE patients. Most
7 of my patients participated in various HAE
8 clinical trials. Many of them involved and
9 benefitted tremendously from the treatment using
10 ecallantide for their acute HAE attacks.

11 I personally witness how access to end
12 prudent use of this remarkable medicine aborted
13 and controlled their otherwise disabling severe
14 attacks. This medicine provided perhaps the most
15 dramatic improvement in many of my patients
16 suffering from their HAE attacks.

17 At this time, however, there are no
18 approved medicines for HAE patients for their
19 acute attacks. Despite the recent approval of the
20 C1 esterase inhibitor for prophylaxis, many of my
21 patients are not able to meet the criteria to
22 receive regular C1 esterase infusion for

1 prophylaxis.

2 Even for patients who are on C1 esterase
3 inhibitor for prophylaxis, many of them may still
4 have occasion to have breakthrough attacks.

5 There is an urgent need for such a
6 medicine which can quickly relieve and abort HAE
7 attacks. Without such a medicine, many of my
8 patients are living in the constant threat and
9 fear of another potentially life-threatening HAE
10 attack, which may result in a few days, even a
11 week of agony.

12 Many attacks require emergency room
13 visits and even hospitalization, intubation and
14 intensive care stay, not only costly, but also
15 emotionally and physically draining.

16 The HAE patient community would be better
17 served by the approval of an urgently needed and
18 potentially life-saving medicine for their acute
19 attacks, such as ecallantide.

20 Thank you.

21 DR. CALHOUN: Thank you.

22 Next on our list is Janet Long.

1 MS. JANET LONG: Good afternoon. My name
2 is Janet Long and I am Vice President of the
3 United States Hereditary Angioedema Association.
4 I thank you for providing HAE patients with an
5 opportunity to discuss the critical need for a
6 safe and effective non-steroidal HAE therapy.

7 I do not have financial ties to Dyax. I
8 am not a shareholder, and the HAE Association paid
9 for my travel here today.

10 This afternoon, I'll be wearing two hats.
11 I will begin by providing a perspective from my
12 vantage point as an officer of the U.S. Hereditary
13 Angioedema Association, the organization that
14 represents well over 6,000 HAE patients in this
15 country.

16 Because I am also a patient and have a
17 story that represents what is experienced by
18 people afflicted with HAE, I will following
19 recount the suffering, fear and frustration that
20 accompanies an arduous journey in search of HAE
21 diagnosis and treatment.

22 Perhaps the best characterization of how

1 HAE affects patients appeared in a 1996 New
2 England Journal of Medicine article.

3 I quote, "Patients with a deficiency of
4 C1 inhibitor are not just an interesting model for
5 study, they are critically ill and many have
6 ancestors who died suddenly from suffocation.
7 Patients live in constant dread of
8 life-threatening laryngeal obstruction," end
9 quote.

10 Ladies and gentlemen, three young,
11 vibrant members of our HAE community have
12 succumbed to that very life-threatening laryngeal
13 swelling just this past year. The absence of an
14 approved acute attack therapy for hereditary
15 angioedema leaves an unmet medical need in its
16 wake.

17 While 17 alpha alkylated anabolic
18 steroids are useful for HAE prophylaxis in certain
19 adults, the scientific literature reveals that
20 many patients continue to experience periodic
21 acute abdominal and laryngeal attacks,
22 notwithstanding ongoing therapy.

1 Moreover, the utility of these potent
2 male hormone derivatives is limited because they
3 are not well tolerated by women, are directly
4 linked to increased serum lipid levels and their
5 use is contraindicated for children, many of whom,
6 tragically, are severely affected and suffer
7 frequent attacks.

8 We're delighted the committee will be
9 considering ecallantide today. The clinical
10 evidence shows that it is an effective medicine
11 that will serve to save lives and ameliorate
12 dreadful morbidity associated with excruciating
13 abdominal and life-threatening laryngeal attacks.

14 Now I'll quickly put on my patient hat
15 and discuss my personal experience.

16 The story of my lifelong struggle with
17 HAE begins at age seven, with severe abdominal
18 attacks and to this day, I am haunted by the face
19 of my mother, who was only able to offer me a hot
20 water bottle to put on my stomach and a few baby
21 aspirin, which she knew would do nothing to ease
22 my suffering.

1 referred persevered until she got to the bottom of
2 my illness and came up with a diagnosis of
3 hereditary angioedema. I was prescribed androgens
4 and, like every female patient, I endure their
5 embarrassing and horrible side effects.

6 Today, you have before you an abundance
7 of clinical (inaudible).

8 DR. CALHOUN: Okay. Thank you.

9 Next is Michelle Williamson.

10 MS. WILLIAMSON: Good afternoon. My name
11 is Michelle Williamson. I do not have any
12 financial ties to Dyax. I'm not a shareholder,
13 and the HAE Association paid for my travel here
14 today.

15 I'm one of the hundreds, if not thousands
16 of HAE patients for whom 17 alpha alkylated
17 androgens are not effective. In addition, I'm a
18 living, breathing example of why HAE patients in
19 the United States desperately need an acute attack
20 therapy.

21 During 23 long years of androgen therapy,
22 I've suffered through countless emergency room

1 At age 21, I experienced an abdominal
2 episode that was so severe it caused internal
3 bleeding, which led to an unnecessary exploratory
4 laparotomy and days in the intensive care unit.

5 Laryngeal attacks came next, completely
6 closing my airway. I saw scores of doctors who
7 either admitted to being totally baffled or
8 offered diagnostic theories that never hit the
9 mark.

10 I tired of showing up to the emergency
11 room only to be sent home after being told that
12 nothing could be done and I would have to learn to
13 live with my condition.

14 I remember vividly one night, a very
15 devastating abdominal attack and curled up in
16 agony. I told my husband, "I don't know if I will
17 make it through the night. Please tell my three
18 beautiful girls that I love them."

19 Finally, after almost 40 years of
20 horrific suffering, with the prospect of living
21 getting bleaker and the attacks continuing
22 unabated, a gastroenterologist to whom I was

1 visits, many of which involved compromised airway,
2 resulted in more than a dozen intubations, and one
3 emergency tracheotomy.

4 The tragedy that almost took my life this
5 last February illustrates why the HAE patient
6 community -- keep in mind patients who obtain
7 relief from androgens are still prone to
8 breakthrough attacks -- need access to an acute
9 therapy.

10 I took a brief vacation to the Rocky
11 Mountains just for the weekend. I had what can
12 only be described as an idyllic getaway. That was
13 until HAE cruelly asserted itself.

14 While driving to the airport to catch a
15 return flight home, I realized I was experiencing
16 a laryngeal attack and it was coming on fast. My
17 boyfriend noticed that my voice pitch had changed.
18 I was beginning to have difficulty breathing and
19 swallowing, so we flagged down a police officer
20 who was able to call an ambulance.

21 At the emergency room, despite my
22 objections, the doctors treated me with medicines

1 HAE patients know do not work, epinephrine and
2 Benadryl. They also tried fresh-frozen plasma, to
3 no avail.

4 The advance of the swelling attack and
5 the baffled look on the faces of the ER physicians
6 made me fear for my life. I prepared myself to
7 die, again. I told my boyfriend to tell my son
8 that I loved him -- he also has HAE -- and that I
9 was sorry; for him to call my mom, call my
10 sisters.

11 As I lay helpless with my airway
12 tightening, I remember coughing and then nothing
13 else. I spent the next seven days intubated and
14 sedated. My lungs had collapsed. I lost the use
15 of my leg muscles from being bedridden. I could
16 barely manage to sit up until day 11. I managed
17 to take three steps that day and I hyperventilated
18 and I fainted.

19 I woke up hearing the doctors trying to
20 decide whether or not to intubate again and
21 telling me I should consider a permanent
22 tracheotomy. After 19 days in the hospital and an

1 \$80,000 bill, I was sent home with antibiotics to
2 treat hospital acquired pneumonia and I endured
3 weeks of rebuilding leg muscles so I could walk
4 again.

5 The tragedy is this traumatic and costly
6 situation could have been completely avoided if an
7 acute attack therapy, like ecallantide, had been
8 available.

9 So as you deliberate approving the Dyax
10 product today, I kindly ask you to consider HAE
11 patients like me who so desperately need this
12 life-saving therapy.

13 Thank you.

14 DR. CALHOUN: Thank you.

15 Our last presentation is by Jenna Long.

16 MS. JENNA LONG: Hello. My name is Jenna
17 Long. I do not have any financial ties to Dyax
18 and the HAE Association paid for my travel to come
19 here today.

20 As we all know, HAE is a genetic
21 condition that runs in families. And I am the
22 16-year-old daughter of Janet Long. I am here to

1 provide a teenager's point of view of what it is
2 like to have HAE and to discuss my experiences
3 with ecallantide, the medicine that you are
4 evaluating today.

5 I had my first HAE attack when I was nine
6 years old. I remember walking into the kitchen,
7 where my entire family was gathered, and being
8 greeted by sudden silence and concerned looks. It
9 was obvious to my parents that my face was
10 swelling and the next thing I knew, my mom was on
11 the phone to the hospital talking to an allergy
12 specialist who treats HAE.

13 Despite my mom's best efforts to calmly
14 describe HAE to me when I was nine years old, I
15 recall being scared and also wondering how this
16 disease would affect me as I grew up.

17 It was frightening to know that my mom
18 had to know right away if I had a funny feeling in
19 my throat or I was having trouble swallowing or
20 breathing. It was very scary to know that an HAE
21 throat attack was dangerous, because it made me
22 worry if there would be enough time to get to the

1 hospital before the swelling would stop me from
2 breathing.

3 My mom recognized the fear and
4 uncertainty brought by HAE was affecting me a lot.
5 So she did some research and found out about trial
6 medications and then enrolled me in an ecallantide
7 clinical trial.

8 Ladies and gentlemen, it was great to
9 know that my mom could take me to the hospital,
10 where I could be given medicine to stop a horrible
11 stomach attack or to make sure that my throat
12 would not swell to the point where I could no
13 longer breathe. Having ecallantide alleviated my
14 fear.

15 I have had several throat attacks since
16 being enrolled in the ecallantide trial, including
17 one in which my tongue swelled so big I couldn't
18 talk. On each occasion that I received
19 ecallantide, I felt better within a half an hour.
20 I was also amazed at how fast the medicine reduced
21 the swelling I was experiencing.

22 I am very grateful to have a medicine

1 that can actually help me, although I do still
2 feel bad knowing that my mom had to suffer all
3 those years without any treatment at all. Knowing
4 that a medicine like ecallantide will be available
5 makes me feel hope and lifts my spirits, because
6 now living a normal life, just like my friends, is
7 possible.

8 Having an effective therapy for attacks
9 means I can participate in school activities
10 without fear that an attack might threaten my
11 life. Also, I can consider going away to college,
12 something that would not have been possible
13 without a medicine like ecallantide.

14 Having ecallantide available to treat HAE
15 attacks has changed my life. Knowing that this
16 medicine is available has greatly eased my fear of
17 pain and death. There are thousands of HAE
18 patients, including young people just like me, who
19 also deserve to live a normal life. I ask you to
20 consider us while discussing the approval of
21 ecallantide.

22 I thank you.

1 for the public hearing representatives? Okay.

2 The open public hearing portion of this
3 meeting has now concluded and we will no longer
4 take comments from the audience.

5 The committee will now turn its attention
6 to address the task at hand, which is the careful
7 consideration of the data before the committee, as
8 well as the public comments.

9 So at this point, we'll begin the panel
10 discussion portion of the meeting. It's open to
11 public observers, but, again, public attendees may
12 not participate, except at the specific request of
13 the panel.

14 So there are some residual questions
15 perhaps left over from the sponsor presentation.
16 There are some residual questions left over from
17 the FDA presentation. And there may be some
18 issues that have come up with respect to the open
19 public hearing presentations. So let's take care
20 of those first and after that, then we'll move on
21 to discuss questions.

22 Dr. Honsinger?

1 DR. CALHOUN: Okay. Thank you.

2 On behalf of the committee, let me thank
3 each of the patient representatives for reminding
4 us of how profoundly this disease can affect your
5 lives. Thank you.

6 Are there questions for any of the public
7 hearing speakers from the committee? Dr. Terry?

8 DR. TERRY: I think it was Ms. Long who
9 was a representative of the foundation. I wanted
10 to ask, has the Dyax Corporation contributed
11 financially in any way to the HAE Foundation,
12 whether it's in terms of financial aid in
13 recruiting patients or in any other form?

14 MS. JANET LONG: No. There has been none
15 of that. I believe there has been an educational
16 grant that is normally collected by the HAE
17 Association at our conferences whenever
18 pharmaceutical companies come. We welcome them
19 all as a product-neutral organization, and they
20 normally fund us with an educational grant for
21 that conference for our patients.

22 DR. CALHOUN: Are there other questions

1 DR. HONSINGER: I have three questions,
2 one for the FDA.

3 This drug is being approved for orphan
4 drug status. Educate us a bit about orphan drug
5 status.

6 Will approval of this drug hamper
7 approval of any other drugs that will be used to
8 treat this orphan disease? That is, we know that
9 there are kallikrein receptor inhibitors in the
10 works as well, and will drugs like that still be
11 able to come afore as an orphan drug?

12 The second question I have is about
13 off-label use. This drug could well be useful for
14 other diseases. We certainly see some patients
15 who have angioedema that's life-threatening that
16 don't have the C1 inhibitor deficiency, and a few
17 of those have been reported in Europe.

18 We see patients who have a
19 kallikrein-related disease when they have
20 angioedema after using angiotensin converting
21 enzyme inhibitors, the blood pressure drugs.

22 The third question is why was it chosen

1 to give three doses at three sites rather than a
2 single dose to these patients?

3 DR. CHOWDHURY: I will take the questions
4 1 and 2 and then ask my colleagues to respond to
5 Question 3.

6 As far as the Question 1, which is for
7 orphan drug status, the orphan status is
8 determined based on the number of patients that
9 are there with the disease in the country.

10 So these are for rare diseases with a
11 certain number of patients, which is small. As
12 far as other drugs coming to the market for an
13 orphan indication, the answer to that question is
14 other drugs can come to the market, even if they
15 target the same pathway or different pathways.

16 The point that comes with the orphan
17 indication, as far as other drugs coming to the
18 market, has to do with exclusivity. If a drug is
19 approved for which clinical studies are required,
20 which is true for any new drugs, then for that,
21 the companies would get exclusivity.

22 For an orphan indication, the duration of

1 exclusivity is longer, longer by about two years
2 compared to a normal orphan drug.

3 What that does is a generic cannot come
4 for that duration. So that is all the orphan
5 indication would do as far as other drugs coming
6 to the market. A generic drug, which is the same
7 drug, a duplicate copy, will not be coming to the
8 market for two or three years. Other drugs can
9 come.

10 The second question is off-label use.
11 Off-label use is recognized and like this drug, if
12 it is to be approved, or for other drugs,
13 off-label use can happen.

14 We understand that, we acknowledge that,
15 and that really has no direct implication on the
16 safety and efficacy for this drug for the
17 indication that we are discussing here. If you
18 have any specific concerns about off-label use, we
19 certainly would like to hear that and understand
20 what the concerns are.

21 So the third question, I'll turn it over
22 to the team.

1 DR. LIMB: I believe it was delivered as
2 three separate injections because the solution
3 comes as a 10 milligram per milliliter solution,
4 and injections greater than one milliliter in size
5 would be more painful to the patients. So I think
6 it was a patient comfort issue. I don't know if
7 the company has anything else they'd like to add.

8 DR. PULLMAN: No, that's exactly how we
9 approached it in terms of the known tolerance of
10 subcutaneous injections to keep it below 1.7 mils.
11 So it was pragmatic to give it as three separate
12 injections.

13 DR. CALHOUN: Dr. Schatz?

14 DR. SCHATZ: Two questions. I think I'll
15 ask them one at a time.

16 The first is Larry Borish came up with,
17 to me, a very astute observation and a hypothesis
18 that there was a relationship between efficacy and
19 baseline severity that seems to be testable in the
20 entire dataset.

21 I wondered whether that, in fact, was
22 tested either by the company or the FDA; that is,

1 a relationship between worst C1 esterase -- or
2 between baseline C1 esterase percent functionality
3 and eventual efficacy.

4 DR. LIU: We have backup slides to show
5 that.

6 DR. SCHATZ: I'm sorry?

7 DR. LIU: We have backup slides to show
8 that.

9 Can we go to 21?

10 So this plot is for change of MSCS versus
11 baseline MSCS. The X-axis is baseline MSCS. The
12 Y-axis is change of MSCS. So the Y-axis is the
13 primary efficacy endpoint we're interested in.

14 The legend is not that big, but the
15 R-square measures the correlation between the
16 primary efficacy endpoint and the baseline. So
17 R-square of one indicates perfect correlation,
18 perfect linear correlation, and R-square close to
19 zero indicates random distribution of Y on X. And
20 from the results, this shows the correlation
21 between Y and X is almost random.

22 Does that answer the question?

1 DR. CALHOUN: No. That's not the
2 question, I don't believe.
3 DR. LIU: Oh, sorry.
4 DR. SCHATZ: No. The question was the
5 relationship of efficacy to baseline C1 esterase
6 inhibitor level.
7 DR. LIU: Oh, sorry, I got that question
8 wrong. We don't have slides to show that. We
9 didn't do analysis for the C1 inhibitor.
10 DR. SCHATZ: And I gather the company
11 doesn't have those data either.
12 DR. HORN: No. Baseline C1 severity
13 doesn't predict the severity -- baseline C1 level
14 doesn't predict the severity of individual
15 attacks. So what we do have is the efficacy based
16 on the severity of attack for the single attack,
17 but not by C1 levels in the patient.
18 DR. SCHATZ: Right. But I'm not so sure
19 that that excludes the hypothesis that baseline C1
20 esterase level would predict responsiveness.
21 DR. HORN: Right.
22 DR. SCHATZ: And that hasn't been tested;

1 DR. LIU: There is subgroup analysis on
2 attack location and I think one of the sponsor's
3 slides showed that, and we can go back to that
4 slide again.
5 DR. SCHATZ: And I know that it showed
6 that it looked like different sites made a
7 difference, but I'm not totally sure that that's
8 the same as using the entire data, or maybe it is,
9 using the entire dataset to look at everybody who
10 had laryngeal aspects of their symptom, but only
11 look at the -- I think that slide might have been
12 total MC, whatever it is, total symptom scores in
13 those patients.
14 But maybe you could clarify what that is,
15 what that was, and see if there we need more.
16 DR. HORN: So you're right. That is
17 patients with a laryngeal attack, their composite
18 MSCS. We have done the analysis of MSCS looking
19 by attack location and severity and we can show
20 you that information for the laryngeal attacks.
21 Slide up, please.
22 So then in this slide, we see the change

1 is that correct?
2 DR. HORN: No.
3 DR. SCHATZ: My second question -- I'm
4 sorry.
5 DR. LIMB: I was just going to add that I
6 think Dr. Borish and you have raised a good point
7 and that's something that the agency is interested
8 in looking at specifically, is the C1 inhibitor
9 level and how it correlated to responses.
10 I think we were coming at it from an
11 approach where we didn't think that it predicted
12 individual severity at baseline, but certainly it
13 could affect response to treatment.
14 DR. SCHATZ: And then my second question
15 is, clearly, the most potentially severe are the
16 laryngeal effects.
17 Has an analysis been done -- if the
18 indication was made just for laryngeal attacks,
19 would your efficacy data -- have you done the
20 analysis and, if not, I would suggest perhaps it
21 could be done, to see whether, with that specific
22 site, whether the efficacy could look more robust.

1 in MSCS score at four hours by laryngeal attack
2 location, by severity, and this is in the
3 integrated Phase 3 numbers.
4 And in here, again, the numbers are
5 small, but we see for moderate attacks, the
6 ecallantide group has a median of minus one and
7 the placebo group has a median of minus .5, and,
8 in severe attacks, ecallantide still has an MSCS
9 change of minus one and placebo is minus 0.7.
10 DR. CALHOUN: Dr. Gruchalla?
11 DR. GRUCHALLA: I have a question, but
12 I'm not sure it can be answered.
13 The patients had to present within eight
14 hours of an attack; is that correct? Okay.
15 Did we see any greater effectiveness if
16 it was given early on? But, again, I don't know
17 if there's enough data. I mean, again, can --
18 We did see that? Oh, we did see that,
19 and it did. Okay.
20 DR. CALHOUN: Dr. Proschan?
21 DR. PROSCHAN: I wanted to get back to
22 the imputation for a second.

1 I guess how I interpret the imputation
2 depends, in part, on whether it's reasonable that
3 this drug could actually prevent -- not just treat
4 the existing problems, but prevent future ones, at
5 least short term. And I'm wondering if there's
6 any data to that end.

7 So if you believe that this drug can
8 actually prevent occurrences, then imputing for
9 those people who get emergent symptoms seems like
10 it does the right thing; that is, it assesses
11 whether the drug helps at preventing. But I don't
12 know if there was already some reason to believe
13 that it might not just treat, but prevent.

14 DR. HORN: Slide up, please.

15 So this was the slide from the core
16 presentation which looked at emerging symptoms
17 after study drug administration, and the top three
18 are patients who had emerging symptoms following
19 ecallantide and the bottom are the patients who
20 had emerging symptoms following placebo.

21 So there are fewer people with emerging
22 symptoms following ecallantide administration than

1 DR. HENDELES: Three questions. The
2 first one is why wasn't a crossover design used
3 since this is a drug with a two-hour half-life
4 and, presumably, patients' episodes are separated
5 by at least a week or more?

6 And the second question is did anybody
7 calculate the number needed to treat to prevent
8 one intubation or some morbidity marker like that?
9 And third, is there any pharmacogenomic data in
10 these patients as to who responds or doesn't
11 respond?

12 DR. PULLMAN: We chose a standard
13 parallel group approach as being the most
14 efficient way to provide evidence of effectiveness
15 over time, given the unpredictable nature of the
16 attacks and the need to provide intervention on a
17 randomized basis.

18 So that was our decision based on
19 pragmatic considerations. But I take your point,
20 and crossover designs could have been considered,
21 but we decided not to approach it that way.

22 DR. HENDELES: Given the small number of

1 following placebo administration.

2 Now, the other thing to consider is that
3 the imputations that we're talking about for the
4 primary analysis, including only emerging symptoms
5 within the first four hours of treatment and only
6 medical interventions within the first four hours
7 of treatment, and the numbers there are very
8 small.

9 For example, in EDEMA4, for emerging
10 symptoms, there were two patients in the
11 ecallantide group and four patients in the placebo
12 group. In EDEMA3, there were zero patients in the
13 ecallantide group and two patients in the placebo
14 group with emerging symptoms.

15 A few more for medical interventions.
16 For EDEMA4, there was one medical intervention in
17 the ecallantide group and nine in the placebo
18 group. And for EDEMA3, there were three in the
19 ecallantide group and five in the placebo group.
20 So the numbers with imputation for the primary
21 endpoints are very small.

22 DR. CALHOUN: Dr. Hendeles?

1 patients available, it would have certainly
2 increased the power of your analysis.

3 My recommendation is if you do any
4 future -- any additional studies, that you
5 consider that study design.

6 DR. PULLMAN: Okay. Thank you.
7 With respect to calculating the rate to
8 minimize laryngeal attacks, no, we have not done
9 that. And pharmacogenomics, likewise, we don't
10 have any information on that. There are about 150
11 discreet mutations affecting the gene and the C1
12 esterase, but it is an interesting question.

13 DR. CALHOUN: Dr. Carvalho?

14 DR. CARVALHO: I just wanted a little bit
15 of clarification on a couple of things. We've
16 learned from EDEMA2, I believe, that the dose
17 information that we got from that study is what we
18 have used with 30 milligrams subcue for the
19 subsequent studies, including pediatric patients.

20 Is that correct?

21 DR. PULLMAN: Yes, that's correct.

22 We have that supported by population PK

1 analysis, in addition to EDEMA2. So the overall
2 dataset from an efficacy perspective is EDEMA2
3 supported by population PK from EDEMA0, 1, 2 and
4 the healthy subject studies.

5 DR. CARVALHO: So once we've established
6 that dose, I am wondering if there's any kind of
7 weight-based or body surface area-based types of
8 data that we can get, for instance, for the
9 incidence of anaphylaxis, since we've learned that
10 immunoconversion and anaphylaxis do not
11 necessarily correlate.

12 Is there any information from the size of
13 the person and the dose that they're getting for
14 immunoconversion, anaphylaxis, and effect?

15 DR. PULLMAN: On effect, we've looked at
16 cuts by weight and I can review that data. On
17 immunogenicity seroconversion, no, we don't appear
18 to have any profile data.

19 And on the overall effect of weight on
20 exposure, within that age cohort that we've
21 studied, the 10 through 78, we did not see weight
22 as a covariant affecting clearance and, therefore,

1 That calculation or that analysis is done if you
2 look in the bottom part.

3 And there you see for weight less than
4 200 pounds, there were 47 patients treated with
5 ecallantide, 45 patients treated with placebo.
6 The median change for the ecallantide group was
7 minus 1.0; for the placebo group, it was minus
8 0.3, and a highly significant P value.

9 For weight greater than 200, where the
10 numbers were smaller, we see the same treatment
11 effect, minus one and minus 0.2, but, again,
12 because of the smaller numbers, the statistical
13 significance is not there.

14 We have also analyzed adverse events by
15 weight and apparently we don't have a slide on
16 that right now. But again, in the overall adverse
17 event profile, we don't find any changes between
18 the under 200 and the over 200 nor do we see
19 any -- like Dr. Pullman said, we don't see an
20 increase in hypersensitivity or anaphylaxis or
21 even seroconversion when we look at it that way.

22 DR. CALHOUN: Dr. Hubbard?

1 clearance would not affect exposure.

2 At the heavier body weights, it may slow
3 up and increase lag time for the initial
4 absorption phase. I can speak to -- well, I'll
5 let Dr. Horn actually speak to the efficacy data
6 we've looked at by body mass index above and below
7 30, as well as weigh above and below 200 pounds.
8 But if you'd like to see that, we can pull that
9 data up.

10 DR. HORN: Okay. So slide up, please.

11 So we evaluated weight with two
12 parameters in mind. One was to look at the
13 question of obesity and one was to try to drill
14 down into some of the pediatric data.

15 So our first proposed cut was to look at
16 weights from less than 100, 100 to 200, and
17 greater than 200. But when we did that, when we
18 ran our data, we found that even though we had the
19 25 pediatric patients, we only had two of those
20 who weighed less than 100.

21 So that analysis wasn't run. It was just
22 run as the less than 200 and greater than 200.

1 DR. HUBBARD: Yes. For the sponsor,
2 while you're still here, I have a couple of
3 questions.

4 First of all, was there any additional
5 safety data from the compassionate use patients
6 that you've given it to that might be of interest
7 to us?

8 DR. HORN: We've had a total of eight
9 patients receive compassionate use. Their safety
10 profile is similar to overall.

11 DR. HUBBARD: Okay. A second question is
12 do you have any data on reduction in steroid use
13 in patients who have received ecallantide versus
14 placebo?

15 DR. HORN: No, and we haven't looked at
16 that, and that is because the studies were
17 measured for acute attacks. So in the attacks,
18 the patient could be on whatever their baseline
19 was.

20 So some patients were on androgens and
21 some patients were not on androgens. And even
22 those that are followed in the open-label study,

1 we haven't followed whether or not they were
2 switched off androgens or started on androgens.
3 DR. HUBBARD: Okay. And then, lastly,
4 have you done any pharmacoeconomic modeling of
5 what the impact of this may be?

6 DR. HORN: Not that I'm aware of. I
7 mean, we do have a significant burden of illness
8 study that we conducted with the HAE Association,
9 which shows a very high financial burden and
10 psychosocial burden to patients with HAE, but as
11 yet, we don't have any evidence of how this will
12 be affected by ecallantide treatment.

13 DR. CALHOUN: Dr. Hoidal?

14 DR. HOIDAL: I just want to push that
15 idea of trying to identify objective indicators of
16 response. And so the question is do you have any
17 information on genotypic variability in relation
18 to response or any indication of any environmental
19 factors, age, anything that might interact with
20 genotypic variability in terms of response?

21 DR. HORN: So we have not found any.
22 We've looked at age in the pediatric population,

1 the adult population, the geriatric population.
2 On both extremes, the numbers are very small, but
3 treatment effects and safety profiles seem to be
4 the same.

5 We've looked at weight, we've looked at
6 gender, we've looked at the antibody status, we've
7 looked at prior exposure to ecallantide, and in
8 all those subgroup analyses, we see a consistent
9 similar effect.

10 It's not too surprising in terms of
11 genomics and pharmacokinetics, is this is a
12 protein, so there is really no CYP enzyme
13 involvement.

14 So you wouldn't expect any of those kind
15 of genetic variabilities or genomic variabilities
16 to make a difference in that. So we haven't
17 identified any group of patients that either have
18 a better response to ecallantide or do not respond
19 to ecallantide.

20 DR. CALHOUN: Dr. Hendeles?

21 DR. HENDELES: Two questions. The first
22 one, is there any relationship between the serum

1 concentration and response? And the second
2 question I have for Dr. Limb is how is the C1
3 inhibitor used and how effective is that at
4 preventing laryngeal attacks?

5 DR. PULLMAN: I'm sorry. Your first
6 question was on pharmacokinetic/pharmacodynamic
7 relationships with respect to response?

8 DR. HENDELES: Actually, serum
9 concentration of the drug in relationship to
10 response.

11 DR. PULLMAN: Okay. And we have not seen
12 one. We haven't conducted an extensive
13 pharmacokinetic analysis with respect to outcome
14 measures in the EDEMA3 and EDEMA4 trials. We did
15 not collect pharmacokinetic samples.

16 And so early attempts at
17 pharmacokinetic/pharmacodynamic relationships were
18 based, in the initial EDEMA0 and EDEMA1 trial, on
19 markers like plasma kallikrein and I think it was
20 C2 levels. But we have not looked at the
21 relationship between drug exposure and effect,
22 except in EDEMA2. So that's the basis of the dose

1 selection.

2 DR. HENDELES: Given a 30 milligram dose,
3 what's the range of concentrations, P
4 concentrations that you would get in adults?

5 DR. PULLMAN: In and across the age range
6 that we've studied, the coefficient of variation
7 is approximately 25 percent. The Cmax
8 concentration is approximately 600 micrograms per
9 mil or 80 nanomolar, and the area under the curve
10 is approximately 3,000, again, with the same
11 coefficients of variation.

12 DR. HENDELES: But in that Cmax, what's
13 the variation between -- what's the range of
14 concentrations? Is it four-fold, eight-fold,
15 two-fold?

16 DR. PULLMAN: I would have to get back to
17 you on that one, but I think it's much less than
18 that. It's relatively tight. I might be able to
19 come back to you later in the session on that.

20 DR. CALHOUN: Dr. Schatz?
21 I'm sorry.

22 DR. LIMB: So getting to your question

1 about the C1 inhibitor product. So the C1
2 inhibitor product reduces the frequency of
3 attacks. I don't have that number in front of me
4 right now. We don't have any comparative
5 information of how this drug might possibly
6 compare to that.

7 DR. RIEDL: Could I speak to that,
8 please, because I know the data?

9 The C1 inhibitor product, with all due
10 respect, the FDA slide is incorrect. The approved
11 C1 inhibitor product is a plasma-derived product.
12 It's not the recombinant product.

13 The plasma-derived C1 inhibitor product
14 that was approved, that study showed it reduced
15 acute attacks by 60 percent, but it's very clear
16 that there are patients that continue to have
17 acute attacks, even while receiving prophylactic
18 C1 inhibitor.

19 DR. CALHOUN: Thank you.

20 Okay. Now, Dr. Schatz.

21 DR. SCHATZ: Again, trying to understand
22 this big difference in post versus pre sample size

1 adjustment, time to treatment appears to affect
2 effectiveness.

3 Has the time between onset of attack and
4 treatment been compared in the post versus the pre
5 sample size change?

6 DR. HORN: Yes. So we have just run that
7 analysis and we showed this slide where there was
8 a zero to two, two to four, four to six-hour
9 cutoff and the six to eight-hour cutoff, showing
10 that the first three groups had a similar response
11 and the latter group had a similar response to
12 ecallantide, but also a much higher placebo
13 response.

14 So when we look at that analysis, there
15 are some changes, some shifts within the first
16 three groups, but a very similar proportion of
17 patients in the pre -- in the 52 and the 44 were
18 in the six to eight-hour treatment group.

19 DR. SCHATZ: So that distribution isn't
20 really different in the two pieces.

21 DR. HORN: No.

22 DR. CALHOUN: Finally, Dr. Terry.

1 DR. TERRY: I wanted to ask a further
2 question about EDEMA4 and the pre/post adjustment.

3 I noticed that in EDEMA3, compared to
4 EDEMA4, there were more patients who had
5 previously had ecallantide, and I assume that
6 means then that they were in EDEMA1 or EDEMA2.

7 What I wanted to ask, then, about EDEMA4
8 is those six outlier placebo patients. I wanted
9 to ask, were they part of prior studies or not?

10 DR. HORN: We have looked at the patients
11 identified as outliers by the FDA and looked at
12 the demographics of those patients specifically.

13 Slide up, please.

14 We have limited our evaluation to the
15 five patients that were included in the final 44
16 patients and not included the sixth patient who
17 was actually included in the first 52. But when
18 you look at these patients -- it's a very busy
19 slide, but if you look down, it's the fourth row
20 up from the bottom.

21 It's prior treatment with ecallantide.

22 You see two of these patients had received prior

1 treatment with ecallantide and three had not. The
2 first patient ending in 03 had not. The patient
3 ending in 02 had. And the patient ending in 05
4 had not. The patient ending in 06 had. The
5 patient ending in 01 had not.

6 Similarly, we look, there are three
7 females and two males. Looking at these patients,
8 we can't find anything in their demographics that
9 would suggest they would have a better or worse
10 response to ecallantide.

11 The one thing we did note, that when you
12 look at the number of symptom complexes present,
13 that four of the five had more than one symptom
14 complex, where, in the overall program, it's
15 closer to half of the patients have a single
16 symptom complex.

17 So that's one thing we have identified in
18 these outliers. But in our analysis, whether or
19 not you have one or more symptom complexes doesn't
20 affect your response.

21 DR. CALHOUN: Okay. We're now going to
22 move on to the questions, of which, as you've

1 heard, there are five. I want to review the
2 voting procedures for the committee.

3 We will be using the new electronic
4 voting system for this meeting. Each of you have
5 three buttons on your microphone, yes, no and
6 abstain.

7 Once we begin the vote, please press the
8 button that corresponds to your vote. After
9 everyone has completed their vote, the vote will
10 be locked in.

11 The vote will then be displayed on the
12 screen. I will read the vote from the screen into
13 the record and then we will go around the room and
14 each individual who voted will state their name
15 and vote into the record, as well as the reason
16 why they voted as they did.

17 Now, just to clarify that a little more,
18 the vote that you make on your microphone can be
19 considered a provisional vote. The official vote
20 will be the vote that you record when you speak
21 your vote. And so if the debate or the arguments
22 around the table as we discuss change your mind,

1 you are free to do that.

2 With that, we'll start with Question 1,
3 which is to discuss the hypersensitivity and
4 anaphylaxis data and provide recommendations for
5 further evaluation, if necessary.

6 Dr. Adkinson?

7 DR. ADKINSON: So I thought I might take
8 this point to share with the panel my own
9 assessment of the hypersensitivity reactions and
10 the implications for the future of this drug and
11 then see where some of my other colleagues who are
12 knowledgeable in this area may agree or disagree
13 as a way of moving forward here.

14 It's clear, I think, to all of us that
15 hypersensitivity reactions represent the major
16 toxicity of this treatment, which otherwise
17 appears to be helpful and efficacious, to some
18 degree, in some patients.

19 And it's not surprising that this is a
20 problem for this drug, because it is a foreign
21 protein, a synthetic protein and has not been seen
22 by the immune system before and, like other

1 foreign proteins that are used as drugs, will
2 almost invariably produce an immune response in
3 some patients who receive it.

4 I'm impressed, from the data that we've
5 been shown, that this is a drug that is highly
6 immunogenic compared to other drugs that
7 infrequently induce an immune response. This drug
8 seems to induce it quite frequently and I think
9 that the estimates that we've been given are
10 probably underestimates.

11 One reason for believing is a report of
12 the IgE assay showing 13 percent response with IgE
13 antibody, but only 1.6 percent response with a
14 so-called neutralizing antibody, which presumably
15 is the major immunoglobulin class IgG antibody.

16 I'm not aware of any exceptions that have
17 been studied in existing drug products that are
18 foreign proteins in which it is not the case that
19 IgE antibody responses in the absence of IgG
20 antibody responses are extremely rare and almost
21 impossible to find.

22 So I think that tells us that this

1 screening assay for IgG is probably insufficiently
2 sensitive to pick up all of those who are
3 sensitized to the drug. That's just the
4 immunogenicity aspect of it.

5 The fact that 13 percent make an IgE
6 antibody response suggests that this is a pretty
7 potent immunogen, considering the fact it's not
8 delivered in a repository fashion or administered
9 with an adjuvant. So like other drugs of this
10 type, aprotinin being a well studied example, one
11 can expect hypersensitivity reactions based on
12 immunological sensitivity.

13 The dose response curve that we've been
14 nicely presented with suggests that even with
15 these insufficiently sensitive assays, we can
16 project up to 60 or 70 percent immune response
17 rate, suggest that that rate really may approach
18 100 percent if we had sensitive enough assays.

19 So this is a drug that's probably going
20 to sensitize most patients who receive it
21 repeatedly, and the chances of having an antibody
22 response that can mediate a severe allergic

1 reaction depends on a number of factors, not the
2 least of which is the frequency with which
3 patients are treated.

4 So like for a bee sting allergy, many
5 patients tolerate a single insect sting once a
6 year. It's the year in which they get a second
7 sting two months into the season that they have a
8 severe anaphylactic reaction, because the
9 preceding antibody response has not had a chance
10 to attenuate.

11 We know, again, from drugs like
12 aprotinin, that over time, when a product is not
13 used, both the G and the E antibody responses go
14 down and patients may be tolerant of the drug in
15 the future.

16 But this is unpredictable in the case of
17 HAE patients because their episodes are
18 unpredictable and, therefore, there is a need I
19 think to be able to assess the risk for these type
20 of potentially life-threatening reactions in
21 patients who are candidates for therapy at a
22 particular point in time.

1 that time patients who are clearly at substantial
2 risk for having an immunologically mediated
3 serious reaction.

4 I'm a little concerned about the use of a
5 re-challenge program to establish patients who are
6 prior reactors as being able to tolerate a
7 subsequent treatment with the drug if by
8 re-challenge we mean just giving the patient who
9 had a previous systemic allergic reaction one
10 milligram of the protein subcutaneously and
11 waiting to see whether they have anaphylaxis.

12 That's a very crude and, in my judgment,
13 unacceptable way of risk assessment because it
14 subjects patients to serious potential for harm
15 just from the reassessment procedure itself. And
16 I think we can do better than that over time by
17 looking at the sero status or the skin test status
18 of patients who are treated after multiple
19 encounters.

20 The other thing that seems, to me, that
21 is almost invariably going to be the case is that
22 the frequency of these reactions is going to

1 So I'm a little concerned about the use
2 of this product without a very stringent risk
3 assessment program that is able to identify at
4 least some, if not most of the patients who are at
5 risk for potentially seriously life-threatening
6 and maybe even fatal allergic reactions.

7 And this should be possible, because we
8 know what the cause of these reactions is. It's
9 either IgG or IgE or some combination thereof and
10 we can measure these things. So this is
11 technologically within the capability.

12 The complexity comes with the biological
13 variation and that's why there's no current
14 correlation between seroconversion, for example,
15 and these reactions that have been observed. But
16 that doesn't mean that these aren't the causal
17 pathways that are involved.

18 So I would encourage development of a
19 risk assessment program that would enable patients
20 who are candidates for repeat therapy with this
21 product to have some type of assessment, which
22 would help to eliminate from further treatment at

1 increase with increasing usage of the licensed
2 product.

3 So that the estimates we have today are
4 likely to be much greater, both proportionately
5 and in terms of absolute number, once this product
6 is on the market for a number of years.

7 And so a proactive effort to get a handle
8 on this risk and to minimize it is essential, in
9 my mind, to coming up with a favorable
10 risk-to-benefit ratio for the treatment of a given
11 patient at a particular point in time.

12 DR. CALHOUN: Dr. Borish?
13 I'm sorry. Dr. Ballow?

14 DR. BALLOW: I agree with my colleague.
15 I think we need to know a lot more about the
16 nature of these IgE and IgG antibodies. A
17 proportion of these reactions occurred with first
18 exposure; is that correct? What proportion?

19 DR. ADKINSON: The way I read what we've
20 been given, all but one of these acute
21 reactions -- my reading of the literature, of the
22 data we've been given, is that all but one of

1 these acute reactions occurred in patients who
2 previously were treated.

3 DR. BALLOW: Who were previously treated?

4 DR. ADKINSON: Treated, yes.

5 DR. HORN: If we specifically look at the
6 eight patients considered potential anaphylaxis,
7 three of those have had prior treatments. One was
8 on the fourth episode, one was on the sixth
9 episode, one was on the 17th episode. The
10 remaining have all been on first dose exposure.

11 DR. BALLOW: Okay. So with that
12 information, then, or possibly, it means that
13 there may be some cross-reactivity.

14 And again, it brings up the similar
15 reactions that were reported in the New England
16 Journal of Medicine with cetuximab, in which there
17 was a regional difference in reaction rate,
18 presumably due to some cross-reacting antigen that
19 was occurring in these individuals who
20 subsequently got this monoclonal antibody.

21 So I think we need a lot more study about
22 the nature of the IgE and IgG antibodies and why

1 they're occurring, presumably, on first exposure.

2 DR. ADKINSON: I don't deny the
3 usefulness of those studies, but I'm also
4 unwilling to believe there's not a stronger
5 correlation if we had adequately sensitive
6 immunoassays for both G and E. I think we're
7 underestimating the previous -- the antecedent
8 immune response in the patients who have had acute
9 reactions.

10 DR. BALLOW: The other question I wanted
11 to ask was in this particular yeast, is there any
12 other drug that's been formulated -- that's your
13 question, I know. I'm, I stole it.

14 Is there any other pharmaceutical that's
15 been produced in this particular yeast using
16 similar recombinant technology?

17 DR. LEE: Kathy Lee, with the Food and
18 Drug Administration. I'm the primary product
19 reviewer on this drug.

20 Yes, there have been other products
21 formulated with *Pichia pastoris*.

22 DR. BALLOW: What's the data with regard

1 to hypersensitivity or reactions?

2 DR. LEE: I can't really speak to that,
3 because it's a variety of different molecules and
4 it would be a matter of going through the data.
5 And I'm not a clinician. I'm a biochemist.
6 Sorry.

7 DR. CALHOUN: Dr. Borish?

8 DR. BORISH: I was, first of all, struck
9 by the fact that five of the eight episodes occur
10 on the first dose. The other thing that's,
11 frankly, striking is that we're talking about IgE
12 and IgG and there's no correlation with IgE and
13 IgG with these episodes.

14 People have IgE and don't react. The
15 people reacting don't have IgE, either by assay or
16 skin test. I mean, to me, this is screaming
17 anaphylactoid and anaphylaxis, which makes me
18 think that I disagree somewhat with what
19 Dr. Adkinson said, that this is not a
20 hypersensitivity reaction.

21 Further exposure may, in fact, not
22 increase the rate. What you see in the first dose

1 may be what you get with this drug.

2 Now, it's possible that there's
3 preexisting IgE to excipients or yeast products
4 that we need to pursue, although I think the IgE
5 to those would have shown up in the assays and
6 didn't. Maybe we need better assays.

7 But there are, frankly, to me, obvious
8 reasons why there could be anaphylactoid effects.
9 This is a protease inhibitor. It was designed to
10 inhibit one specific protease, but you know
11 there's off-target effects. I know of one
12 off-target effects, patients' PTTs were prolonged.

13 That's not because it's blocking
14 kallikrein. I suspect there are probably some
15 proteases out there that might be connected to
16 some ITIMs on the MASO. Maybe Dr. Chowdhury knows
17 this field, I don't. But I suspect that we're
18 seeing a pharmacological anaphylactoid effect and
19 it may, in fact, not progress with further use.

20 DR. CALHOUN: Dr. Gruchalla?

21 DR. GRUCHALLA: Couldn't that be tested
22 by basophile histamine release or a MASO assay of

1 some sort? Or maybe that's already been done for
2 non-specific --

3 DR. BORISH: And I would just put in the
4 record that doing that on the MASO would be a
5 totally appropriate request.

6 DR. CALHOUN: Do we have summary of
7 recommendations then that we can give to the
8 agency for what further needs to be done in terms
9 of the evaluation of these immunologic responses?

10 DR. GRUCHALLA: One more point.

11 DR. CALHOUN: Rebecca?

12 DR. GRUCHALLA: One more point.

13 Regarding back to one of your questions about the
14 types of antibodies, you could do inhibition
15 assays with various parts of the molecule to see
16 if it's actually reacting to a certain part. So
17 just, again, when you're doing those, do
18 inhibition assays to get more information.

19 DR. CALHOUN: Dr. Ballow?

20 DR. BALLOW: So you are asking for
21 recommendations about going forward, what kind of
22 assays should be utilized?

1 DR. CALHOUN: Dr. Schatz?

2 DR. SCHATZ: If one were to do immediate
3 type skin testing routinely in a group of patients
4 and if there were enough of them, one would get
5 some idea then of the sensitivity and specificity
6 of that as a predictive tool.

7 DR. CALHOUN: So that actually goes to
8 Dr. Borish's comment that we don't know what the
9 predictive value of a positive IgE serum, or
10 positive IgG, nor skin test is for the
11 manifestation of anaphylactic or anaphylactoid
12 reactions to this agent.

13 DR. ADKINSON: I don't think I would
14 state it that way. I think we do know that IgE is
15 a risk factor for anaphylaxis and that we are
16 administering -- we're talking about administering
17 a foreign protein to a patient with an antecedent
18 IgE antibody response.

19 There definitely is a substantial
20 increase in risk of a systemic reaction. It's not
21 100 percent, but it's a finite number, and we're
22 talking about life-threatening reactions here.

1 DR. CALHOUN: I was just trying to
2 crystallize specific recommendations to the agency
3 that they could use in their planning process.

4 DR. BALLOW: I think some of them were
5 stated before. I think you have to look at
6 assays -- well, you have to improve on the basic
7 assays of IgE and IgG, as Dr. Adkinson alluded to,
8 and the other is to look at mediators.

9 I mean, tryptase is perhaps one, maybe
10 some complement components, because if it's
11 anaphylactoid, maybe there's evidence of
12 complement activation as another possible pathway,
13 and there may be other mediators that might be
14 important.

15 DR. CALHOUN: Dr. Carvalho?

16 DR. CARVALHO: One more thing that may be
17 worthwhile to start looking, and this is more of a
18 potential hematologic thrombotic kind of concern,
19 but to go ahead -- and because of the homology of
20 the drug with the tissue factor initiator, perhaps
21 getting studies for that, as well, in addition to
22 the IgEs and the IgGs for the other components.

1 It's not trivial minor reactions.

2 We do know that's a risk factor. There
3 may be other mechanisms involved, but it seems to
4 me that when we're dealing with a foreign protein
5 and we know is highly immunogenic, that we need to
6 deal first with the immunologic reactions.

7 DR. FOGGS: Another long-term
8 recommendation. Invariably, since these drugs
9 come to market will be associated, as has been
10 mentioned, with increased numbers of episodes of
11 anaphylactoid or anaphylactic reactions, is
12 establishing a prophylactic protocol akin to what
13 we have utilized in association with radio
14 contrast media?

15 I think a preemptive strike by
16 establishing such a protocol as the data is
17 generated will be most useful.

18 DR. CALHOUN: Okay. Next is Question 2.
19 This is a voting question. It comes in two
20 pieces. The adult piece is 2-A and the pediatric
21 piece is 2-B.

22 So the question is do the data provide

1 substantial and convincing evidence that
2 ecallantide provides clinically meaningful
3 beneficial effect on acute attacks of hereditary
4 angioedema in patients 18 years of age and older?

5 So you can vote your conscience at this
6 point for 2-A, 2-A for the adults.

7 DR. PROSCHAN: Given that most of the
8 analyses were done in the entire group, not
9 separately for 18 years and older, to me, it seems
10 like it might be a more useful question to ask,
11 first of all, did they show benefit in this
12 overall group, and then, secondly, is there
13 sufficient evidence to make a separate conclusion
14 or the same conclusion for the 10 to 17.

15 DR. CALHOUN: I don't disagree with you.
16 The questions came from the agency and we need to
17 give them advice, I guess, in the context of their
18 structure.

19 Is that fair?

20 So again, this is Question 2-A, do the
21 data provide substantial evidence of efficacy in
22 patients 18 years of age and older?

1 At some point, these will be locked in.
2 I guess as long as they're flashing, you can
3 change your vote. There's one person who has not
4 voted, apparently.

5 Do we have 18? Yes, okay.

6 The results are yes, eight; no, four; one
7 abstention. That counts 13. I misspoke and said
8 18 earlier. There are 13 voting members. Sorry.

9 So, Dr. Hoidal, perhaps we can start with
10 you and we'll work around the table.

11 DR. HOIDAL: John Hoidal. I voted no.
12 This is a difficult decision for me, but in the
13 end, I was concerned -- the issue of substantial
14 and convincing, I didn't think the bar was met.

15 I was concerned of some uncertainty of
16 overall efficacy and robustness of response,
17 without an adequate explanation for the striking
18 differences between the pre and post on the EDEMA4
19 study and without -- and with a fairly modest
20 response in the EDEMA3 study with the switch of a
21 couple of patients in terms of robustness.

22 DR. CALHOUN: Thank you.

1 Dr. Gruchalla?

2 DR. GRUCHALLA: I actually voted yes. I
3 agree that the efficacy could be greater.
4 However, I feel like the data was strong enough.
5 I am concerned about the hypersensitivity issues
6 and feel that in addition to looking at the
7 efficacy issues, that the hypersensitivity issue
8 needs to be evaluated over time.

9 DR. CALHOUN: And we will come to that
10 with safety.

11 I neglected to ask each member to state
12 their name and their vote prior to their comments.

13 Dr. Terry?

14 DR. TERRY: Peter Terry. I voted no.
15 And the reason I voted no is, first of all, for
16 EDEMA3, I didn't consider it robust when the
17 change of two patients could make that much
18 statistical difference.

19 And for EDEMA4, the extension seems to be
20 so much different in terms of distribution of
21 clinical presentation and these unusual outliers,
22 that I'm not convinced that it would be

1 representative of a much larger sample.

2 DR. BORISH: Lawrence Borish. I voted
3 yes. For an orphan disease, I don't think we're
4 ever going to enroll enough patients to generate
5 enough statistics to robustly satisfy every
6 objection that can be raised.

7 My teaching in statistics is that you
8 pick a primary aim, you pick a statistical plan,
9 you do it and you live and die by your primary
10 aim. We don't do retrospective analyses of
11 secondary and tertiary endpoints or subgroup
12 analyses, nor do I think should we do that in our
13 statistical analysis. They met their primary aim
14 and I voted yes.

15 DR. CALHOUN: Dr. Carvalho?

16 DR. CARVALHO: Paula Carvalho. I also
17 voted yes. And again, I echo Dr. Borish's
18 comments. Again, with an orphan disease, this is
19 a tough one and this is also not a minor
20 inconvenience. This is a very deadly condition.
21 And 18-year-old and older is very similar, in my
22 mind, to an adult.

1 Also, these are the people that are going
2 to be either within the end of puberty, within
3 some of the risk factor times in their lives in
4 which some of these events may be accelerating.
5 So I voted yes.

6 DR. CALHOUN: Dr. Hendeles?

7 DR. HENDELES: I voted no. I don't think
8 it met the criteria.

9 If I had been asked does it show any
10 efficacy, I probably would have voted yes, but
11 substantial -- I forgot the exact wording, but I
12 was not convinced, because especially in EDEMA4,
13 if you look at the pre-group before the extension,
14 the response to the drug was similar in both
15 groups, but it was the shift in the placebo group
16 that really created that statistically significant
17 effect.

18 And there were an awful lot of -- on the
19 data plot, there were an awful lot of patients
20 that had response on placebo and there were also
21 patients who were in the active treatment group
22 that had minimal response. So it was not

1 treatment was proper and the intention to treat
2 is, in fact, in this case, not the right way to
3 analyze the data.

4 On EDEMA4, I am intrigued scientifically
5 by the variation between the first and last groups
6 of patients. Collectively, the study is
7 convincing to me.

8 The post hoc analysis I think probably
9 raises lots of very interesting biological
10 questions, which absolutely need to be addressed,
11 and I think the questions of immunogenicity that
12 Dr. Adkinson raised, the issues of dosing that
13 Dr. Borish raised are very important. But
14 collectively, I think EDEMA4 is a strong study.
15 So I voted yes.

16 Dr. Schatz?

17 DR. SCHATZ: Well, obviously, I found
18 this decision difficult. I couldn't make it. But
19 my abstention is pending further evaluation of the
20 current data. It's clear that the need is
21 overwhelming.

22 But still the question of efficacy or

1 convincing to me.

2 DR. CALHOUN: Dr. Adkinson?

3 DR. ADKINSON: Franklin Adkinson. I
4 voted yes. I thought that the criteria for
5 efficacy was acceptable and voted yes because I'm
6 not convinced that additional studies or larger
7 numbers are going to change this relatively weak
8 effect for a very complex disease.

9 DR. CALHOUN: I'm Bill Calhoun. I voted
10 yes. This is an orphan drug for a rare disease.
11 So echoing Dr. Borish's comments, I think that it
12 will be logistically and practically very
13 difficult to do a study that would provide
14 definitive, substantial and convincing efficacy.

15 EDEMA3, the reason I asked the question I
16 did about how and when the error was detected was
17 had the error been detected sometime down the
18 line, I would have been substantially skeptical,
19 but this was really a technical violation, not
20 really even a misrandomization. It was really a
21 technical error, a clerical error.

22 And so I think, in fact, the analysis by

1 effectiveness, which seems, to me to be, as you
2 can tell from my other questions, so much related
3 to the difference in the second study, between the
4 second phase and the first phase.

5 I think that, number one, looking at the
6 symptom scores with just three levels instead of
7 five would be useful and I certainly would like to
8 see a relationship of effectiveness to baseline C1
9 esterase inhibitor levels before, then, I would be
10 able to answer this question as to whether I think
11 enough of an effectiveness burden has been shown.

12 The need is overwhelming, but we do need
13 to be able to show that it's an efficacious
14 medicine.

15 DR. CALHOUN: Dr. Ballow?

16 DR. BALLOW: Mark Ballow. I voted no,
17 mainly because I'm really bothered by EDEMA4 study
18 between the difference -- between the pre and post
19 sample sizes.

20 There has to be an explanation. In fact,
21 if we were going under Robert's Rules of
22 regulation, I would have voted to table this whole

1 notion until we got better information back,
2 perhaps an analysis like Dr. Borish proposed,
3 looking at the C1 esterase inhibitor functionality
4 and trying to correlate that with response.

5 At this point, for me, it's really
6 difficult to tell about efficacy because I' really
7 bothered about the two sets of data between the
8 pre and the post sample size.

9 DR. CALHOUN: Dr. Honsinger?

10 DR. HONSINGER: Richard Honsinger. I
11 voted yes. We have a drug that's less than
12 perfect, does not always work, has problems with
13 hypersensitivity, but it's the only thing we have
14 for this orphan disease and it looks like, at
15 least some of the time, it works.

16 DR. CALHOUN: Dr. Foggs?

17 DR. FOGGS: Michael Foggs. I voted yes.
18 I think it's been pointed out time and time again
19 during this session that there is a compelling
20 need for acute treatment for hereditary angioedema
21 and even though this treatment is less than
22 perfect, I think on a compassionate basis, I was

1 with continuous outcomes, it might have come out
2 even more striking.

3 But I don't think the company did
4 anything nefarious. I think they probably just
5 ran out of the very sickest patients and then the
6 next group of patients is less sick and for some
7 reason, the treatment does better in those.

8 So I'm convinced by that analysis that
9 this treatment helps some people. If the
10 treatment didn't help anyone, then even if they
11 had done something nefarious, they couldn't have
12 made it come out significant.

13 The imputation didn't bother me quite so
14 much because I do think it makes some sense to do
15 the imputation they did. Even though it came out
16 making the drug look better, I think that might be
17 a fair thing to do if it is preventing additional
18 emergent events.

19 The two given the wrong treatment, I
20 mean, in a small study like this, if you switch
21 the labels of patients, then, of course, it's
22 likely that it will change the results. So I

1 personally obligated to vote yes.

2 I'm somewhat impressed by the fact that
3 of those patients who did respond, greater than 50
4 percent of them responded within a two-hour
5 period, and certainly, that's comforting for those
6 patients who are experiencing flares of hereditary
7 angioedema.

8 I would like to have seen better data and
9 more data, but because of the reasons so stated, I
10 voted yes.

11 DR. CALHOUN: Dr. Proschan?

12 DR. PROSCHAN: Michael Proschan. I voted
13 yes. This was really close for me. And I really
14 am voting yes on the question that I said, which
15 is, was there an effect in the overall group.

16 By far, the thing that bothered me the
17 most was the pre/post difference in the fourth
18 study and, I mean, that's a big difference. And
19 the FDA's analysis showed that there was a
20 treatment by time pre and post interaction.

21 That was using a test that's harder to
22 find an interaction. If they had done something

1 agree that it's not a robust result, but I don't
2 think you can really get a super robust result
3 with the numbers of patients that we're talking
4 about.

5 Then the last issue, the number of tests
6 issue that you brought up, it does bother me that
7 sometimes they present a pooled analysis, while
8 sometimes they present the separate results, and
9 then they also presented an analysis stratified by
10 certain things which made it look even better.

11 But there I think the company made a
12 mistake in not making the primary analysis
13 stratified anyway. When you stratify the
14 randomization, the sensible thing to do is also to
15 stratify the analysis in the primary analysis.

16 So it wasn't strong, to me, but it was
17 enough to tip the scales for me.

18 DR. CALHOUN: Okay. That concludes our
19 vote on Question 2-A.

20 Dr. Hendeles, you have a comment?

21 DR. HENDELES: I just made the
22 observation that most people voted what they

1 thought the agency should do, not what the
2 question was.

3 The question was, is whether it has
4 substantial and convincing evidence. If you
5 listen to what everybody said, they -- well, I
6 just think they changed the question.

7 DR. CALHOUN: Point taken. With that,
8 we'll move to Question 2-B.

9 Do the data provide substantial and
10 convincing evidence that ecallantide provides a
11 clinically meaningful beneficial effect on acute
12 attacks of hereditary angioedema in patients 10 to
13 17 years of age? Once again, your options are
14 three; yes, no and abstain. And perhaps you can
15 let us know when we have 13 rung in.

16 Okay. This time, we'll start at the
17 other end of the table. Dr. Proschan, you're
18 first.

19 DR. PROSCHAN: I voted no simply because
20 I don't believe that with this amount of data, you
21 can really separate out and say, okay, in this
22 group of 10 to 17, there was a differential

1 children are any different in this disease than
2 adults and that their response should be any
3 different than those over 18.

4 In addition, these people have no other
5 therapy. We're talking about a drug that has a
6 very short half-life, a very short action, and I
7 agree that the company needs to and should be
8 compelled -- if released for children, should be
9 compelled to collect data, when it can, on
10 children's use of this drug.

11 DR. CALHOUN: Dr. Ballow?

12 DR. BALLOW: Mark Ballow. Responding to
13 the strict wordage of the question, there is not
14 enough -- there is obviously not enough data to
15 substantiate efficacy.

16 DR. CALHOUN: Dr. Schatz?

17 DR. SCHATZ: Michael Schatz. I agree
18 it's a different question as to whether we would
19 expect that group to respond any differently, but
20 I would have to agree the data are not adequate to
21 show it.

22 DR. CALHOUN: Bill Calhoun. I also voted

1 effect.

2 So I can't tell whether, in that young
3 group, there would be a different effect or not.
4 So they didn't show convincingly in that subgroup,
5 but I don't think they would be able to do that.

6 DR. CALHOUN: Dr. Foggs?

7 DR. FOGGS: I voted no for the age group
8 of 10 to 17 because the limitations of the data
9 were too great. I think that there were some
10 convincing data with the 18 and over group. Even
11 though it was not extremely convincing, it was
12 somewhat convincing. I cannot make that statement
13 about the 10 to 17 age group.

14 DR. CALHOUN: Dr. Honsinger?

15 DR. HONSINGER: Richard Honsinger. I
16 voted yes. It's going to be difficult to collect
17 children and children's data. Children often
18 don't get diagnosed early. They often don't show
19 up with the disease until their mid or their late
20 teens.

21 It's going to be difficult to collect
22 that data. And I have no reason to think that

1 no. There were four children in randomized
2 double-blind placebo-controlled studies, which is
3 not enough data to be convincing nor compelling.

4 Dr. Adkinson?

5 DR. ADKINSON: Franklin Adkinson. I
6 voted no, based entirely on the numbers.

7 DR. CALHOUN: Dr. Hendeles?

8 DR. HENDELES: I voted no, but; no, based
9 upon the question, but I think the response would
10 probably be the same in that age group.

11 DR. CALHOUN: Dr. Carvalho?

12 DR. CARVALHO: I voted yes. I ignored
13 the verbiage of the question and I went with what
14 I would actually do if I were faced with a child
15 in the emergency room. I would find it difficult.
16 As Dr. Honsinger said, there are not going to be
17 that many of them and I would hate to have an age
18 cutoff in which I was not allowed or able to give
19 a potential medication for a kid.

20 DR. CALHOUN: Dr. Borish?

21 DR. BORISH: Lawrence Borish. I voted
22 yes. If 10 to 17 is an orphan indication within

1 an orphan disease, if we are asking the industry
2 to come up with compelling data in 10 to 17 year
3 olds, it will never happen.

4 Hereditary angioedema in adults and
5 hereditary angioedema in adolescents is the same
6 disease. There is no conceivable reason why a
7 drug that we agree works in adults won't work in
8 adolescents and we have numbers of patients who
9 support that concept.

10 It is conceivable that perhaps some of us
11 can use it off-label, but I suspect it will take
12 an act of God to get an insurance company to
13 approve an off-label indication. So I voted yes.

14 DR. CALHOUN: Dr. Terry?

15 DR. TERRY: I voted no because I
16 literally interpreted the question that we're
17 being asked. I think the data is inadequate.

18 DR. CALHOUN: Dr. Gruchalla?

19 DR. GRUCHALLA: Rebecca Gruchalla. I
20 voted no for the same reasons, for the numbers
21 issue, but I totally agree with Larry Borish. I
22 mean, if the question had been worded differently,

1 I would have answered yes.

2 DR. CALHOUN: Dr. Hoidal?

3 DR. HOIDAL: John Hoidal. I voted no,
4 for the reasons stated of inadequate data.

5 DR. CALHOUN: Okay. Thank you,
6 Committee, on Question 2.

7 Dr. Borish and Dr. Gruchalla, I think
8 perhaps at the end of the questions, you could be
9 prepared to articulate something in terms of
10 advice or guidance to the agency along those
11 lines. I happen to agree with you, personally, on
12 the orphan indication, but on the basis of the
13 question itself.

14 Our next question is also a voting
15 question. It's also a two-part question.
16 Question 3-A is, "Has the safety of ecallantide
17 been adequately addressed for the treatment of
18 acute attacks of hereditary angioedema in patients
19 18 years of age and older?" Three choices; yes,
20 no and abstain.

21 So we have one not voted? Okay, we're
22 there?

1 The results are five yes and eight no.

2 Dr. Hoidal, can we begin with you?

3 DR. HOIDAL: I voted yes, which is a
4 little tough. It was based on the data that was
5 presented in terms of safety, it was based on the
6 safe use program that was outlined, and it was
7 based on the suggestions that have already been
8 forwarded in terms of the major side effect.

9 DR. CALHOUN: Dr. Gruchalla?

10 DR. GRUCHALLA: Rebecca Gruchalla. I
11 voted no. All I am saying here is that I think it
12 needs to be continually explored and the various
13 assays that we discussed previously employed.

14 DR. CALHOUN: Dr. Terry?

15 DR. TERRY: Dr. Terry. I voted no,
16 because of my concern that we haven't developed a
17 refined method of predicting those who would
18 likely be at risk for anaphylactic or
19 anaphylactoid reactions.

20 DR. CALHOUN: Dr. Borish?

21 DR. BORISH: I defined adequately
22 assessed as assessed adequately to balance the

1 risks of the un-safety of this drug with the risk
2 of this disease. The public testimony was very,
3 very moving in terms of the fact that patients are
4 dying every year of this disease. We can treat
5 anaphylaxis. We can't treat HAE. I think the
6 safety is adequately addressed.

7 DR. CALHOUN: Dr. Carvalho?

8 DR. CARVALHO: I also voted yes. This
9 drug is only to be given in a monitored setting.
10 It's not to be given by self-injection like some
11 of the other agents that patients have available
12 to them at home.

13 For that reason, as long as we're aware
14 of the potential adverse effects, then we should
15 have something in place for us to be able to treat
16 them, and we can treat anaphylaxis in the
17 emergency room.

18 DR. CALHOUN: Dr. Hendeles?

19 DR. HENDELES: I voted no, but, again, I
20 don't think the data is adequate, but I think
21 there's enough to approve the drug. And it
22 reminds of the situation with Xolair, where there

1 was a signal in the original package that expanded
2 with use. And so I just think there needs to be
3 some post-marketing monitoring program to collect
4 that information.

5 DR. CALHOUN: Dr. Adkinson?

6 DR. ADKINSON: I voted no. I continue to
7 be concerned about the risk management program
8 proposed by the sponsor as being inadequate to
9 identify those patients at highest risk for what
10 could be a fatal outcome, which I think is not an
11 acceptable side effect for this drug.

12 DR. CALHOUN: Bill Calhoun. I voted yes.
13 The safety data are adequate. I agree with
14 Dr. Adkinson and Hendeles and others that it is
15 not optimum. It's not complete. It's not where
16 it needs to be. But it's adequate to at least
17 know where we need to be looking for a safety
18 signal as we go forward.

19 Dr. Schatz?

20 DR. SCHATZ: Michael Schatz. I hope
21 people understand that people are saying exactly
22 the same thing, but with different votes.

1 has such a short action. So I voted yes.

2 DR. CALHOUN: Dr. Foggs?

3 DR. FOGGS: I voted no because I think
4 some of the studies that need to be done have been
5 carried out, but to a limited degree.

6 And I think the immunology is
7 sufficiently complex that additional studies need
8 to be done to eliminate the potentially excessive
9 risks, especially as the drug comes to market, for
10 individuals succumbing not only from anaphylaxis,
11 but also from possibly other problems associated
12 with the use of this drug which have not been
13 explored yet, such as the absence of coagulation
14 studies mentioned earlier.

15 DR. CALHOUN: Dr. Proschan?

16 DR. PROSCHAN: Michael Proschan. I voted
17 no. I guess I'm looking to Question 4 as far as
18 the balance of the safety and efficacy. So I
19 voted no.

20 DR. CALHOUN: Okay. That concludes
21 voting on Question 3-A.

22 Dr. Adkinson?

1 Again, it depends on what's adequate. I
2 think it's not adequate to understand everything
3 we'd like to know about it. It may very well be
4 adequate to balance the potential benefits. But
5 that's not how I interpreted the question. So I
6 voted no.

7 DR. BALLOW: Mark Ballow. I voted no. I
8 agree with Dr. Schatz in what he said.

9 The other thing -- now, don't take it as
10 self-evident that medical centers know how to
11 treat anaphylaxis. Many times, they don't
12 satisfactorily treat anaphylactic or anaphylaxis.

13 DR. CALHOUN: Dr. Honsinger?

14 DR. HONSINGER: Richard Honsinger. I
15 voted yes. The question asks if the safety has
16 been adequately assessed. I think we assessed the
17 safety. We found out the drug does have a problem
18 of hypersensitivity.

19 We assessed the drug for cardiac effects
20 with its QT. We assessed it for thrombosis. We
21 assessed it for renal and hepatic effects and did
22 not find other serious effects with this drug that

1 DR. ADKINSON: I voted no, in part, also,
2 because I believe that the potential for creating
3 a hypercoagulable state as a result of the
4 antibodies produced by this product needs to be
5 definitively assessed, and that has not been done.
6 I would not make that a precondition for approval,
7 but I do think it's a safety issue that has not
8 been addressed that needs to be.

9 DR. CALHOUN: Okay. Thank you.

10 So Question 3-B is, "Has the safety of
11 ecallantide been adequately addressed for the
12 treatment of acute attacks of hereditary
13 angioedema in patients 10 to 17?" Question 3-B.

14 Okay, pause. Dr. Hendeles?

15 DR. HENDELES: Would the agency be
16 willing to remove the words "substantial and
17 convincing" from that question?

18 DR. CALHOUN: "Substantial and
19 convincing" are not in 3-B, right?

20 DR. HENDELES: No, four.

21 DR. CALHOUN: We're on 3-B.

22 DR. HENDELES: Oh, I'm sorry.

1 DR. CALHOUN: That's okay. You can be
2 embarrassed a second time.
3 DR. HENDELES: Shut my mouth.
4 DR. CALHOUN: Okay. So we're voting 3-B,
5 the safety in children 10 to 17.
6 We have one vote to come in?
7 Okay. We have 13?
8 For the record, two yes, 11 no, and zero
9 abstentions.
10 I guess we're back to Dr. Proschan.
11 DR. PROSCHAN: Michael Proschan. I voted
12 no. Given how I voted on the previous question,
13 it would have been absurd for me to vote any other
14 way, and given that we know less about the 10 to
15 17 group.
16 DR. CALHOUN: Dr. Foggs?
17 DR. FOGGS: My reason for voting no is
18 the same for the 18 and over group.
19 DR. CALHOUN: Dr. Honsinger?
20 DR. HONSINGER: Richard Honsinger. No,
21 because we do not have any data, but I don't think
22 that this should withhold the drug from market.

1 DR. TERRY: Dr. Terry. I voted no, for
2 the reasons stated.
3 DR. CALHOUN: Dr. Gruchalla?
4 DR. GRUCHALLA: Rebecca Gruchalla. I
5 voted no, for the reasons stated.
6 DR. CALHOUN: And Dr. Hoidal?
7 DR. HOIDAL: John Hoidal. I voted no,
8 for the reasons stated.
9 DR. CALHOUN: Thank you. That completes
10 our voting on Question 3.
11 Question 4 is the last voting question
12 and it goes to the point that Dr. Proschan has
13 mentioned a couple of times. It's the balance
14 between safety and efficacy.
15 Please note. Please note that this
16 question does not split into adults and pediatric
17 age ranges. This is a question that's based --
18 correct me if I'm wrong, Badrul. This is a
19 question based on the proposed label submitted by
20 the sponsor.
21 DR. CHOWDHURY: Yes, that is correct.
22 DR. CALHOUN: Thank you.

1 DR. CALHOUN: Dr. Ballow?
2 DR. BALLOW: Mark Ballow. No, for the
3 similar reasons for part A.
4 DR. CALHOUN: Dr. Schatz?
5 DR. SCHATZ: Michael Schatz. No, for
6 everything that's been said.
7 DR. CALHOUN: Bill Calhoun. No. Total
8 experience of 15 patients.
9 Dr. Adkinson?
10 DR. ADKINSON: No, ditto.
11 DR. CALHOUN: Dr. Hendeles?
12 DR. HENDELES: Leslie Hendeles. No.
13 DR. CALHOUN: Dr. Carvalho?
14 DR. CARVALHO: Paula Carvalho. Yes, for
15 the same reasons as before. Although the numbers
16 may not be there, the concerns, we are well aware
17 of the concerns that we have and my yes is on a
18 philosophical rather than on the verbiage.
19 DR. CALHOUN: Thank you.
20 Dr. Borish?
21 DR. BORISH: Lawrence Borish. Ditto.
22 DR. CALHOUN: Dr. Terry?

1 I have not personally seen the label, but
2 this is based on their proposed indication.
3 Correct?
4 DR. CHOWDHURY: That is correct. It is
5 based on the proposed indication, which covers the
6 age ranges down to 10 years of age.
7 DR. CALHOUN: Okay. Thank you.
8 So Question 4, again, a voting question,
9 "Do the safety and efficacy data provide
10 substantial and convincing evidence to support
11 approval of ecallantide for the treatment of acute
12 attacks of hereditary angioedema?" Three choices;
13 yes, no and abstain.
14 So a point of order and a question to the
15 agency, which --
16 Les, do you want to just articulate what
17 you're suggesting? I don't know to the extent
18 they'll be willing to do that, but you certainly
19 can make the statement.
20 DR. HENDELES: In question number 4,
21 would you be willing to delete the words
22 "substantial and convincing?"

1 DR. CHOWDHURY: As the chair mentioned,
2 we will not be, because that is the standard based
3 on which we take a decision whether to approve a
4 drug or not. Be it the orphan indication or not,
5 there has to be substantial and convincing
6 evidence for us to approve a drug.

7 But keep in mind, you should be voting
8 based on the question the way it is asked, but,
9 again, you can make your comments later on. And
10 for us, it is equally important to hear what you
11 have to say and we take the comments very
12 seriously as we talk about the drug internally for
13 ultimately decision-making processes.

14 DR. CALHOUN: Thank you, Dr. Chowdhury.

15 Okay. So we'll vote Question 4. Please
16 let me know when we have 13.

17 Okay. For the record, we have six yes
18 votes, we have five no votes, and we have two
19 abstentions.

20 And we'll begin with Dr. Hoidal.

21 DR. HOIDAL: I voted no, for the issues
22 earlier expressed regarding the strength of the

1 orphan diseases as any other disease.

2 DR. CALHOUN: Dr. Borish?

3 DR. BORISH: Lawrence Borish. I voted
4 yes, because I considered the data, that it
5 worked, compelling and I considered the safety
6 concerns mitigated by the severity of the disease.

7 DR. CALHOUN: Dr. Carvalho?

8 DR. CARVALHO: Paula Carvalho. I also
9 voted yes, for the same reasons that have been
10 mentioned here before. This is, to me, a little
11 bit different.

12 This is an orphan disease and I know that
13 we have to be held to stringent criteria, but we
14 have very little to offer this in this disease and
15 we are fully aware of the dangers that could
16 potentially exist.

17 I suspect that we'll be looking at those
18 very aggressively. I echo Dr. Gruchalla's comment
19 about that is a must for us to be able to, with a
20 clear conscience, use this agent on people. But
21 my vote was yes.

22 DR. CALHOUN: Dr. Hendeles?

1 data supporting efficacy, the lack of adequate
2 studies in the pediatric population, and the
3 concerns that have been raised about the adverse
4 effects, particularly the anaphylaxis.

5 I would say that's not to say that the
6 standard may be difficult to change or things may
7 be modified in terms of an orphan drug indication.

8 DR. CALHOUN: Dr. Gruchalla?

9 DR. GRUCHALLA: Rebecca Gruchalla. I
10 voted yes. I believe that the efficacy data,
11 again, needs to be strengthened, but, again, this
12 is an orphan disease, a bad disease, and I think
13 the endpoints were met. I do believe that the
14 safety issues need to be continually addressed as
15 you move forward, but, again, I still believe that
16 efficacy outweighs safety.

17 DR. CALHOUN: Thank you.

18 Dr. Terry?

19 DR. TERRY: I voted no, because that's
20 consistent with my prior two votes for safety and
21 efficacy. And I also don't believe that we should
22 have a different standard for evidence related to

1 DR. HENDELES: Leslie Hendeles. I
2 abstained because I couldn't honestly respond to
3 the question the way it was worded. But I believe
4 that there is enough evidence of efficacy and
5 safety and given the compelling need for this drug
6 to provide it, but there needs to be -- and I'll
7 address that later -- the precautions. It
8 shouldn't be administered in a CVS pharmacy.

9 DR. CALHOUN: Dr. Adkinson?

10 DR. ADKINSON: Franklin Adkinson. I
11 voted no, jointly taking into consideration the
12 modest efficacy of this therapeutic product
13 combined with substantial toxicity, which I think
14 has not been minimized by an adequate risk
15 management program.

16 DR. CALHOUN: Bill Calhoun. I voted yes.
17 Again, this is an orphan disease. I'm not
18 convinced that there will ever be truly compelling
19 and convincing data generated. The safety
20 concerns that have been articulated are real,
21 they're important, and they cannot be forgotten.

22 And I think each of the "yes" voters has

1 mentioned that. So, Dr. Adkinson, you're right on
2 the mark there.

3 However, we can treat anaphylaxis,
4 particularly when the drug is provided in a
5 medically supervised setting and, as we've heard,
6 again, very eloquently from the patient
7 representatives, without this drug, people may
8 die.

9 Dr. Schatz?

10 DR. SCHATZ: I abstained, again, for
11 similar reasons as before. I would like to see
12 some additional data before I would want to judge
13 the data. Initial analysis, I should say, as
14 substantial and convincing, I don't think I can
15 say it was substantial and convincing based on
16 what we have so far.

17 But a combination of seeing additional
18 data and still asking a different question, which
19 is do the benefits outweigh the risks, that's
20 still a different question, to me, than would I
21 recommend approval. But I have to abstain based
22 on the information I have so far.

1 situation where a patient's life is at stake.

2 But I really believe we cannot lower the
3 bar, that we need some additional information.
4 There's a lot of discussion about the shortcomings
5 of this study and it needs to be cleaned up.

6 DR. CALHOUN: Dr. Foggs?

7 I'm sorry. Dr. Honsinger? I'm sorry.

8 DR. HONSINGER: Richard Honsinger. I
9 voted yes. I voted yes because I believe this
10 drug -- we have enough evidence to say that it's
11 efficacious. We have problems about the safety,
12 but I'm convinced that for an orphan disease, it
13 could be fatal, and we need the drug.

14 DR. FOGGS: Michael Foggs. I voted no.
15 The precise wording of the question by the FDA
16 actually defines the standards set by the FDA and,
17 to that extent, has been stated. An honest
18 response to that particular question as it relates
19 to the standards set would have to be no.

20 However, if I had the opportunity to
21 separate out the age brackets between the 10 to 17
22 and 18 and over, I would vote yes, because I think

1 DR. CALHOUN: Dr. Ballow?

2 DR. BALLOW: Mark Ballow. I voted no.

3 It's a difficult ethical question. I certainly
4 appreciate the fact that this is a difficult
5 disease to treat. It's an orphan disease and not
6 very many patients.

7 However, we've heard a lot of discussion
8 around the table about difficulty with efficacy
9 and, also, with potential adverse events and I
10 think we cannot lower the bar. The FDA has gotten
11 into trouble before by lowering the bar and it's
12 come back to haunt them.

13 Hopefully, if this drug does not get
14 approved at this particular time, there ought to
15 be other ongoing studies with this particular
16 medication so it will be available to patients.

17 There was a recent approval by the FDA of
18 another "medication," quote-unquote, for use in
19 this disease, although it's not for this
20 particular indication, for acute onset of attacks,
21 I imagine what will happen, if push comes to
22 shove, that it'll be used off-label in a dire

1 the efficacy is sufficient in the upper age
2 bracket as opposed to the lower age bracket, even
3 though I'm not satisfied with the safety for
4 either age bracket.

5 DR. CALHOUN: Dr. Proschan?

6 DR. PROSCHAN: Michael Proschan. I think
7 it's more accurate to say that I voted "you know"
8 as opposed to yes. Yes, slightly ahead of no as
9 opposed to the other way around.

10 It was very close, but I think that in
11 this situation, when there's no other drug that
12 treats it, I do think that they showed some
13 efficacy and I have concerns about safety and, for
14 me, it was just tipped more toward saying yes.

15 DR. CALHOUN: Okay. Thank you. So that
16 concludes the voting on Question 4.

17 The last question before us, number 5, is
18 a discussion question, asking our collective
19 advice on recommendations regarding labeling, risk
20 mitigation strategies for hypersensitivity and
21 anaphylaxis, the potential for
22 self-administration, and any other recommendations

1 you've got for the agency.
 2 Dr. Hendeles, then Dr. Borish.
 3 DR. HENDELES: I think it needs to have a
 4 strong precaution that clearly states that it
 5 should only be administered in a medical facility
 6 where there is personnel and equipment trained and
 7 experienced in handling anaphylaxis.
 8 You laughed when I said CVS, but last
 9 night, I went to get a candy bar and there's a
 10 minute clinic in the CVS here where there's a
 11 nurse practitioner that sees patients for a fee.
 12 So that type of thing could happen, and so I think
 13 it really needs to be something close to an
 14 emergency room facility or an allergist's office.
 15 DR. CALHOUN: Dr. Borish?
 16 DR. BORISH: While I agree, in principal,
 17 while I will request all my HAE patients to have
 18 their episodes between the hours of 8:00 and 5:00
 19 Monday through Friday, they're not always that
 20 cooperative.
 21 In the 200-year history of the University
 22 of Virginia, I don't think any patient has been

1 More immediately, the education of the
 2 patient in the administration of self-administered
 3 epinephrine would certainly be appropriate and I'm
 4 sure would happen.
 5 DR. CALHOUN: Dr. Honsinger?
 6 DR. HONSINGER: Yes. I agree with the
 7 labeling. The labeling needs to warn about
 8 anaphylaxis. It's going to be difficult for these
 9 patients to get to the place, and Dr. Riedl told
 10 us about his case where the patient didn't have
 11 access to the medicine and had a serious outcome.
 12 So I would think that it's something the
 13 patient may well carry and needs to go to a
 14 facility that can treat anaphylaxis to take their
 15 injection.
 16 So it might be any place that's familiar
 17 with giving injections to patients that are at
 18 high risk of anaphylaxis. That's certainly the
 19 allergist's office. It certainly can be many
 20 urgent care centers, if you can get in.
 21 It certainly can be in an emergency room,
 22 where you can actually take it while you're

1 seen in the emergency room in less than six hours
 2 who had a pulse and I don't see that changing.
 3 I think patients with HAE will spend most
 4 of their time trying to convince the ER physicians
 5 not to give them Epi and Benadryl and to actually
 6 give them this drug. I think in the real world,
 7 they're going to get so impatient with the lousy
 8 service they get in emergency rooms, that we're
 9 going to have to find a way to get this drug
 10 administered at home.
 11 As Dr. Riedl said very well, these
 12 patients are driven, they're motivated, they're
 13 intelligent, they know their disease. They can be
 14 taught how to treat anaphylaxis at home.
 15 DR. CALHOUN: Dr. Schatz?
 16 DR. SCHATZ: Relative to anaphylaxis,
 17 relative to the risk mitigation, again, I feel
 18 like a program that evaluates skin testing and the
 19 potential for pretreatment if, in fact, it's
 20 not -- some of these reactions are not IgE
 21 mediated, would help with risk mitigation over
 22 time.

1 waiting in the emergency room and then you're
 2 there for several hours to make sure if you have
 3 anaphylaxis, you'll be seen.
 4 I think that we need to work to develop,
 5 challenge protocols and ways to evaluate it,
 6 whether it be skin tests, whether it be laboratory
 7 tests, for the patients that may be sensitive and
 8 we need to work on what we can do for those
 9 sensitive patients as far as prophylactic therapy
 10 when they receive the drug.
 11 DR. CALHOUN: Dr. Foggs?
 12 DR. FOGGS: I agree that with regards to
 13 labeling, all the patients who are administered
 14 the medication should have auto-injectable
 15 epinephrine at their disposal and be taught
 16 properly how to use it, should it be needed.
 17 With regards to risk mitigation, I feel
 18 strongly that there needs to be a protocol
 19 established as these studies are being carried out
 20 to allow for assessment post-anaphylaxis in a
 21 systematic fashion so that data can be generated
 22 to help define what the reaction is and, also,

1 protocol be set up for potential prophylaxis once
2 patients can be targeted, based upon biological
3 markers or other markers, to identify their high
4 risk for anaphylaxis as a result of taking this
5 medicine.

6 DR. CALHOUN: Dr. Gruchalla?

7 DR. GRUCHALLA: I just have a question.

8 These are one cc injections, subcutaneous
9 injections, right? So trying to get those to
10 be -- a patient to do that to themselves -- I
11 mean, three. That's what I'm saying.

12 Could you do three one -- I mean, I'm
13 just asking the question.

14 DR. BORISH: If I'm not breathing?

15 DR. GRUCHALLA: I mean, again, I'm not
16 saying let's not move towards that, absolutely,
17 but just in concept, because the EpiPen itself is
18 how much? I don't know how much is in an Epi.
19 It's a total of .3.

20 DR. BORISH: But this is subcutaneous.

21 DR. GRUCHALLA: But anyway, it's just
22 something to think about.

1 the shelf life of this drug? Is it months or is
2 it years?

3 DR. PULLMAN: Actually, we recommend it
4 be kept under refrigerated conditions, namely, two
5 degrees to eight degrees. We do have stability
6 data at room temperature that shows the product is
7 within acceptance criteria for up to two weeks.

8 And we have done some cycling, I think
9 cycling from refrigerator to room temperature
10 about five times, and it still has integrity. But
11 we recommend refrigeration two to eight.

12 DR. BALLOW: (Off mic) Expiration date?

13 DR. PULLMAN: There is at least two years
14 stability for the refrigerated moiety.

15 DR. CALHOUN: Okay.

16 I'm sorry. Dr. Borish?

17 DR. BORISH: Just one quick comment under
18 D.

19 If the drug does gain approval, one of
20 the things I would like to see is a post-marketing
21 study in Type III HAE, which is a disease -- as
22 bad as the drugs are in HAE, none of them work in

1 DR. CALHOUN: So a point of data perhaps
2 for the industry, for the sponsor. Is there a
3 solubility concern here? Is 10 milligrams all you
4 can get into one ml or can it be made in a more
5 concentrated solution?

6 DR. PULLMAN: We've actually been
7 actively investigating the solubility issue. It's
8 the solubility versus stability tradeoff. So
9 that's why you have the 10 milligrams per ml. But
10 it looks very feasible that we can push upwards in
11 terms of the concentration probably to 30
12 milligrams per ml. That work is ongoing with
13 external academic centers helping us.

14 DR. CALHOUN: And so at that point, you
15 could get away with a single injection.

16 Dr. Honsinger?

17 DR. HONSINGER: I'd like to ask the
18 industry about stability of this drug. And you
19 mentioned that this drug can be kept out at room
20 temperature for some time and then put back in the
21 refrigerator.

22 How many times can it be done? What's

1 Type III.

2 It's a real disease. I, at this point,
3 may have as many patients with that as I do with
4 Type I and II. And for those who know the
5 disease, this should be effective there and I
6 would love to see a post-marketing study in that
7 disease.

8 DR. CALHOUN: Dr. Adkinson?

9 DR. ADKINSON: I just want to say what
10 I've already said in another way. I think the
11 best approach to maximizing the safety of this
12 product is prevention, not learning how to treat
13 anaphylaxis.

14 And I believe it's within our technical
15 capability of the company and the FDA to assure
16 essentially -- to eliminate, virtually eliminate
17 all IgE dependent anaphylaxis to this product with
18 proper pre-use testing. And that seems, to me, to
19 be achievable and we should do it.

20 DR. CALHOUN: Okay. I'm going to give
21 you a summary of what I've heard from this
22 discussion and then I will invite comment and

1 edits from the committee.

2 So summarizing, I think we all have --
3 first, to say, were we the Supreme Court, Nina
4 Totenberg would talk about a sharply divided
5 decision.

6 In fact, I don't think this was a sharply
7 divided decision. I think this was a unimodal
8 population of opinions in which people came down
9 on different sides of the dichotomous question.

10 But there was quite a bit of homogeneity, I think,
11 of discussion. We just read the issues a little
12 bit differently and voted a little differently.

13 So I don't think you should look at the
14 six to five to two decision as being that the
15 committee couldn't make up their mind. I think
16 you've heard the discussion. I think the
17 committee has given you their advice.

18 So summarizing, I think we've heard that
19 there are some concerns about the relatively
20 modest efficacy, the lack of robustness of the
21 findings. And so to the extent that additional
22 can be brought to bear on that question, that

1 would be helpful.

2 Dr. Hendeles raised the point about
3 perhaps improving the experimental design to make
4 more of the same -- or make more of the patients
5 that we've got access to.

6 There has been considerable discussion
7 about the variable response by population, this
8 first 52 versus last 44 issue, and I think the
9 consensus that I've heard is that all of the
10 committee members would like an intensive digging
11 into the biology that underlies that variability.

12 And there may be some bio samples in a
13 bio bank at the sponsor's area. The agency may
14 well have information in their database that they
15 can search through. But I think trying to
16 understand that difference between those two
17 populations would be extremely important.

18 I think we saw by the vote that the
19 majority of the committee was unconvinced by the
20 amount of data that were provided. So as things
21 go forward, given all of the considerations that
22 Dr. Borish articulated in this regard, the

1 difficulty of generating real information in
2 pediatrics, to the extent that it can be done on
3 the way forward, I think that's certainly a
4 recommendation that the committee would make.

5 There are a number of safety concerns.
6 Dr. Adkinson has articulated these very, very
7 elegantly. The coagulation issues, I think have,
8 in fact, not been addressed at all. The
9 anaphylaxis issue we've talked about quite a bit.

10 I just will say, personally, Frank, I
11 don't know that there's debate about what you said
12 that we ought to prevent anaphylaxis. I think
13 that's exactly right. If we can predict and
14 prevent the anaphylaxis, that's exactly the right
15 strategy.

16 So identifying predictors of adverse
17 responses, whether that represents -- whether that
18 can be accomplished with more sensitive assays for
19 IgE and IgG or other predictors, but you really --
20 the company, the sponsor, needs a predictive
21 biomarker for adverse events, because it is clear
22 that anaphylaxis can kill, can and does kill,

1 maybe just as dead as if you die from an HAE
2 episode.

3 So eliminating the anaphylaxis I think is
4 certainly a priority.

5 So those are the distillates of the
6 discussion that I've heard and I would, at this
7 point, entertain any edits or amplifications.

8 Dr. Borish?

9 DR. BORISH: Is it a reasonable
10 marketing -- is it an appropriate labeling request
11 to ask the company to provide free screening for
12 IgE for patients getting this drug? Because while
13 Dr. Adkinson and I split slightly, I absolutely
14 agree with him that if someone has IgE, you don't
15 want to cavalierly administer the next dose.

16 And people who are getting this dose
17 regularly probably should be screened regularly.
18 It's not going to be available in any laboratory
19 at my institute. The company really are the only
20 people that can do it and, frankly, they should do
21 it.

22 DR. CALHOUN: And to the extent that

1 there might be -- using your venom immunotherapy
2 concept, Frank. The fact that you've got IgE
3 positivity at one point may put one at increased
4 risk, but I think that the predictive value of
5 those tests needs to be ascertained in an
6 objective and an empiric fashion.

7 Dr. Gruchalla?

8 Pardon me. Dr. Chowdhury?

9 DR. CHOWDHURY: Thank you very much for
10 the summary. It was actually very, very helpful
11 for us to hear the comments on the voting and we
12 really appreciate the comments that we have
13 received and also your summary.

14 There's one point I would like to go back
15 and perhaps encourage some discussions, if you
16 could, because we have heard multiple times from
17 Dr. Borish and Dr. Schatz about the C1 esterase
18 levels as a predictive factor and we will
19 certainly go back and look at it.

20 But the question that really we need to
21 get a sense from the committee here is how
22 strongly really the committee feels about the C1

1 esterase levels being predictive of severity of
2 the attack. In other words, if the level is high,
3 is that going to be more severe? If the level is
4 low, is that going to be less severe?

5 Secondly, how stable the C1 esterase
6 level in a particular patient is going to be over
7 time of the disease, because in many of these
8 patients, the time that the C1 esterase levels
9 were drawn in relationship to the drug
10 administration may vary, because I don't think we
11 have a very good handle, from a scientific
12 literature standpoint, of the C1 esterase levels
13 as predictors and we're certainly going to go back
14 and look at it, but we would like to have some
15 discussions around this issue, which would be very
16 helpful to us.

17 Thank you.

18 DR. CALHOUN: Okay. Dr. Schatz?

19 DR. SCHATZ: Well, I was going to say a
20 little bit different. But in answer to that,
21 again, I don't think the company -- I mean, I
22 think the company said that there isn't a

1 relationship between attack severity and C1
2 esterase inhibitor, but that's really not the
3 question.

4 The question is whether there's a
5 difference in responsiveness to the drug based on
6 preexisting levels. So the second questions you
7 asked are important. But that's the analysis that
8 needs to be done and, to my understanding, that
9 hasn't been looked at.

10 DR. BORISH: I was going to make the same
11 comment, because I misspoke earlier and I want to
12 be very clear. C1 inhibitor levels or functional
13 doesn't predict severity or episodes or the nature
14 of episodes or anything like that.

15 I was really wanting to speculate that
16 maybe the patients with the lowest levels, that
17 might predict a responder subgroup. So I want to
18 correct my earlier remarks.

19 DR. HENDELES: Functionality, not
20 whether --

21 DR. BORISH: Yes, functionality may
22 predict response to treatment, not severity.

1 DR. CALHOUN: Dr. Gruchalla?

2 DR. GRUCHALLA: One other thing. I'm not
3 sure how much the skin testing has been explored
4 and does the skin test align with the in vitro IgE
5 results. If they did -- again, I don't know if
6 this is a nonspecific MASO releaser.

7 In that case, then the skin test is not
8 going to be useful at all. But if it were not and
9 it was specific IgE, that would be an easy
10 screening assay, if, indeed, you could get it to
11 work.

12 DR. CALHOUN: Dr. Hoidal?

13 DR. HOIDAL: Just kind of broaden that
14 comment, because you have these striking
15 differences and there's got to be some information
16 there.

17 So just mining the information of all the
18 biologic data, the phenotypic data and see if
19 there's any predictors that you can come up with,
20 because as we move forward, if you could save a
21 substantial portion of non-responders from the
22 risk of anaphylaxis, you'd do them a great favor.

1 DR. CALHOUN: Dr. Honsinger?

2 DR. HONSINGER: Maybe someone else can
3 answer. I don't know that the variability of the
4 C1 esterase inhibitor in a single patient -- we
5 know they're low, but do they go high and low just
6 like complement does? I think we need to also
7 establish that before we hang our hat on that
8 measurement.

9 DR. CALHOUN: Dr. Carvalho?

10 DR. CARVALHO: Just one quick comment for
11 the sponsor. We've heard a lot of the patients
12 tell us, and we've seen this ourselves, where
13 people don't know what this entity is and patients
14 come to the emergency room and they go through all
15 of these things and time is wasted because this is
16 not recognized. Many times, the patients know
17 much more than the physicians about the disease.

18 I would urge the company to make a very,
19 very, very massive educational effort throughout
20 the emergency rooms for teaching hospitals, for
21 community clinics, everywhere, because these
22 patients are going to be out there.

1 encourage medical alert bracelets.

2 The other thing that I do, which is
3 variably helpful, is provide a letter that
4 explains their condition and the treatments,
5 which, up to this point, have been very little,
6 but the treatments that may be available that they
7 can take to the emergency room.

8 The other thing that we try to do at our
9 center is establish a home emergency room where
10 they frequently will -- as closest to their
11 residence, that they will go to.

12 And with an emerging area of medical
13 records, we're hopeful that, in the medical
14 record, there will be a denotation that they have
15 hereditary angioedema, and that would solve this
16 battle that they fight day in and day out to
17 convince people of this rare condition.

18 DR. CALHOUN: Okay. Perhaps,
19 Dr. Chowdhury, I can ask you if there are other
20 aspects that you'd like to hear additional
21 discussion about.

22 Dr. Seymour, Dr. Limb?

1 And if there's something that can be
2 offered -- it's almost going to be analogous to
3 stroke issue with saving cerebral tissue with
4 different treatments that are now available. So
5 anything that's time-based and anything that has
6 the urgency that this has needs a huge educational
7 effort and I would encourage that.

8 DR. CALHOUN: Dr. Gruchalla?

9 DR. GRUCHALLA: Quick comment. Do they
10 wear Medi-Alert bracelets? I mean, that would
11 be -- I mean, the question is -- this is another
12 thing I'm thinking, like mastocytosis patients
13 that come to the emergency room and nobody knows
14 about the disease.

15 What about Medi-Alert bracelets?

16 DR. CALHOUN: Is there a response?

17 DR. RIEDL: If I could have your
18 permission.

19 DR. CALHOUN: Certainly.

20 DR. RIEDL: I don't want to speak for the
21 patients, but I can tell you that in my practice,
22 I care for about 30 to 35 HAE patients and we do

1 DR. CHOWDHURY: No. We think we had a
2 very good discussion around the issue that we
3 wanted to be discussed and it was very helpful for
4 us.

5 Dr. Seymour, Dr. Limb, Dr. Permutt, any
6 other issues?

7 No, we don't. Thank you.

8 DR. CALHOUN: Okay. Well, with --
9 Dr. Hubbard? I'm sorry.

10 DR. HUBBARD: Yes. First of all, I'd
11 like to thank you for an excellent session. And I
12 don't mean to have the last word in a negative
13 way, but as an industry representative, I do have
14 a slightly different role than other folks here
15 and I wanted to make sure I separated my comments
16 from any consideration of ecallantide.

17 I just want to express my concern with
18 the statistical approach to the analysis of the
19 efficacy data, in particular, with the way the
20 efficacy for E4 was analyzed.

21 I'm at a loss to understand why the
22 agency was unwilling to accept the primary

1 endpoint that they agreed to beforehand and was
2 discussed with the sponsor, why they failed to
3 accept the analysis at its face value and went
4 ahead and conducted additional analyses, which I
5 think prejudiced the value of the primary
6 endpoint, which was quite solid.

7 So I just think that it's important that
8 I do express that on behalf of a sponsor. If you
9 do the flip test and if we were to do something
10 like that, I think it would be rowdily disputed
11 and not accepted.

12 So I think it's just important for us to
13 have an understanding of the rules by which you go
14 about doing thorough post hoc analyses of efficacy
15 data so that we can be prepared for this kind of
16 thing should a sponsor come before the agency in
17 the future.

18 DR. PROSCHAN: Could I address that?

19 DR. CALHOUN: Dr. Proschan? Yes.

20 DR. PROSCHAN: I mean, I think in this
21 situation, it's a little bit different, though,
22 because the original sample size was supposed to

1 be 52.

2 It's not like the original sample size
3 was 96 and then they went back and said, okay,
4 let's look at the first half and see if that's
5 different from the second half. There is an issue
6 when you decide to change something midstream,
7 namely the sample size, there is a natural concern
8 about it.

9 DR. HUBBARD: Yes, but, I mean, you
10 agreed to this before they did it, I think.

11 You didn't?

12 DR. CALHOUN: Actually, Dr. Proschan
13 didn't.

14 DR. PROSCHAN: I certainly didn't.

15 DR. CALHOUN: Just point of order --

16 DR. HUBBARD: My understanding is the
17 agency agreed to this.

18 DR. PERMUTT: I have to make two points
19 here. One, we agreed to the original protocol.
20 We agreed to the amendment to the protocol with
21 the condition that this analysis would be
22 performed. So we are doing -- we are presenting,

1 in fact, what was agreed to.

2 Second, I think you've mischaracterized
3 what we've done here. We haven't refused to
4 accept the analysis. We're here asking for
5 advice.

6 We think that this feature of what we
7 observed in our analysis was relevant to the
8 committee's deliberations and, clearly, many
9 people on the committee also thought it was
10 relevant and interesting and important. The
11 decision has yet to be made.

12 DR. ROSEBRAUGH: Let me just add
13 something, also. It is not unusual for us, much
14 like the sponsor would do, to do a lot of
15 sensitivity analysis. Additionally, when we come
16 before a committee, we want them to have the full
17 range of the picture and it would really be unfair
18 of us to not present the full range of the picture
19 to the committee and seek their advice.

20 As Tom just said, that doesn't mean we've
21 rejected anything. We've done sensitivity
22 analysis on a primary on a very small database.

1 That's very appropriate to do.

2 DR. CALHOUN: Dr. Terry?

3 DR. TERRY: Yes. I'd like to ask a
4 question of Dr. Chowdhury.

5 Do you have expectations that orphan
6 diseases as opposed to non-orphan diseases will be
7 analyzed by different standards of evidence and do
8 you have any sort of guidelines for that?

9 DR. ROSEBRAUGH: I'm not Dr. Chowdhury,
10 but I'll take that. No, we don't. Orphan disease
11 does not get a break. So they have to have the
12 same level of evidence that we think it works. I
13 mean, we really don't want to make a Type I error.
14 We do not want to make a Type I error.

15 DR. CALHOUN: Okay. With that, I would
16 like to thank the Dyax folks for their
17 comprehensive presentation. Thanks to the FDA
18 folks for their very, very detailed and
19 insightful, informative analysis.

20 Thank you to the press for your interest.
21 Thank you to the HAE Society and the other members
22 of the speaking team, and many thanks to the

1 members of the committee.
2 We're adjourned.
3 (Whereupon, the proceedings at 3:19 p.m.
4 were concluded.)
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