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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC)

Thursday, June 23, 2011

8:30 a.m. to 4:00 p.m.

Hilton Washington DC/Silver Spring

Silver Spring, Maryland

1 **Meeting Roster**

2 **PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS**

3 **(Voting)**

4 Paul Greenberger, M.D.

5 Professor of Medicine

6 Department of Medicine

7 Division of Allergy-Immunology

8 Northwestern University Feinberg School of Medicine

9 Chicago, IL

10  
11 David Jacoby, M.D.

12 Professor of Medicine

13 Physiology/Pharmacology, and

14 Anesthesiology/Perioperative Medicine

15 Edwards Professor of Pulmonary Medicine

16 Director, OHSU (Oregon Health and

17 Science University) MD/PhD Training Program

18 Vice Chair for Research, Department of Medicine

19 Chief, Pulmonary and Critical Care, OHSU

20 Portland, OR

21

22

1     Jerry Krishnan, M.D., Ph.D. (Chair)  
2     Associate Professor of Medicine and Epidemiology  
3     Director, Asthma and COPD (Chronic Obstructive  
4     Pulmonary Disease) Center  
5     Section of Pulmonary and Critical Care  
6     University of Chicago  
7     Chicago, IL  
8  
9     David Mauger, Ph.D.  
10    Professor, Department of Public Health Services  
11    The Pennsylvania State University  
12    College of Medicine  
13    Hershey, PA  
14  
15    Rodney Mullins (Consumer Representative)  
16    National Director  
17    Public Health Consultants and Advocates  
18    Duluth, GA  
19  
20  
21  
22

1 Thomas Alexander Platts-Mills, M.D., Ph.D.  
2 Director, Asthma and Allergy Disease Center  
3 University of Virginia Medical Center  
4 Charlottesville, VA

5  
6 Kelly Stone, M.D., Ph.D.  
7 Director, Allergy and Immunology  
8 Clinical Training Program  
9 Staff Clinician  
10 Laboratory of Allergic Diseases  
11 National Institute of Allergy and Infectious  
12 Diseases  
13 National Institutes of Health  
14 Bethesda, MD

15  
16 **TEMPORARY NON-VOTING MEMBER**

17 Ellen Strahlman, M.D. (Acting Industry  
18 Representative)  
19 Senior Vice President & Chief Medical Officer  
20 GlaxoSmithKline  
21 Research Triangle Park, NC

22

1       **TEMPORARY VOTING MEMBERS**

2       Larry Borish, M.D.

3       Professor of Medicine

4       University of Virginia Health System

5       Charlottesville, VA

6

7       Michael Foggs, M.D.

8       Chief of Asthma, Allergy, Immunology

9       Advocate Health Centers

10      Chicago, IL

11

12      Jay Portnoy, M.D.

13      Chief, Section of Allergy, Asthma & Immunology

14      Children's Mercy Hospitals & Clinics

15      Kansas City, MO

16

17      Philip Posner, Ph.D. (Patient Representative)

18      Arlington, VA

19

20

21

22

1     Gillian Shepherd, M.D.  
2     Clinical Associate Professor of Medicine  
3     Joan and Sanford Weill Medical College of  
4     Cornell University  
5     New York, NY

6  
7     James Tracy, D.O.  
8     Allergy, Asthma & Immunology Associates, P.C.  
9     Omaha, NE

10  
11    **FDA (Non-Voting)**

12    Joan Buenconsejo, Ph.D.  
13    Acting Statistical Team Leader  
14    Division of Biometrics II  
15    CDER, FDA

16  
17    Badrul Chowdhury, M.D., Ph.D.  
18    Director, Division of Pulmonary, Allergy, and  
19    Rheumatology Products  
20    CDER, FDA

21  
22

1     Susan Limb, M.D.

2     Medical Team Leader

3     Division of Pulmonary, Allergy, and

4     Rheumatology Products

5     CDER, FDA

6

7     Brian Porter, M.D., Ph.D., M.P.H.

8     Medical Officer

9     Division of Pulmonary, Allergy and

10    Rheumatology Products

11

12    Curtis Rosebraugh, M.D.

13    Director, Office of Drug Evaluation II

14    CDER, FDA

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

2                   (8:33 a.m.)

3                   **Call to Order**

4                   **Introduction of Committee**

5                   DR. KRISHNAN: Good morning, everybody. I  
6 would like to go ahead and get started, so if you  
7 want to take your seats, I'd appreciate it.

8                   I'd like to welcome everyone to the FDA  
9 Pulmonary-Allergy Drugs Advisory Committee meeting  
10 on June the 23rd. As everyone knows, we're going  
11 to be discussing an application for approval for a  
12 drug to treat hereditary angioedema. We're going  
13 to start off first with introduction of the  
14 committee members, and I'd like to start to my  
15 right to the very end.

16                  Dr. Strahlman, if you could please introduce  
17 yourself and your perspective. Thank you.

18                  DR. STRAHLMAN: Good morning, I'm Dr. Ellen  
19 Strahlman. I'm the chief medical officer for  
20 GlaxoSmithKline, and I'm acting industry  
21 representative on the panel today.

22                  DR. BORISH: Larry Borish. I'm a professor

1 of medicine in the allergy immunology division at  
2 the University of Virginia.

3 DR. STONE: Kelly Stone, I'm a staff  
4 clinician in the laboratory of allergic diseases,  
5 NIAID, NIH and run the fellowship program and the  
6 consult service there.

7 DR. PLATTS-MILLS: I'm Tom Platts-Mills, and  
8 I'm a professor of medicine at the University of  
9 Virginia, and I study allergy and immunology.

10 DR. SHEPHERD: Gillian Shepherd. I'm a  
11 clinical associate professor of medicine at Cornell  
12 in New York, allergy and immunology.

13 DR. GREENBERGER: Paul Greenberger,  
14 professor of medicine, Northwestern University,  
15 division of allergy immunology.

16 DR. TRACY: Jim Tracy, practicing allergist,  
17 Omaha, Nebraska and associate professor at  
18 Creighton University.

19 DR. POSNER: Philip Posner. I'm the patient  
20 rep. I have MS and also suffer from edema  
21 secondary to allergic response to bee and wasp  
22 stings.

1 DR. MAUGER: David Mauger, I'm a professor  
2 of biostatistics at Penn State University, and my  
3 area is clinical trials design and analysis.

4 DR. KRISHNAN: My name is Jerry Krishnan.  
5 I'm the chair of the Pulmonary-Allergy Drugs  
6 Advisory Committee, and I direct the Asthma and  
7 COPD Center at the University of Chicago.

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

10 MR. MULLINS: My name is Rodney Mullins.  
11 I'm national director of Public Health Advisors and  
12 Consultants.

13 DR. PORTNOY: Jay Portnoy. I'm a professor  
14 of pediatrics at the University of Missouri Kansas  
15 City School of Medicine and chief of allergy at  
16 Children's Mercy Hospitals and Clinics in Kansas  
17 City, Missouri.

18 DR. JACOBY: David Jacoby. I'm chief of  
19 pulmonary and critical care and vice chair of the  
20 department of medicine at Oregon Health and Science  
21 University in Portland.

22 DR. FOGGS: I'm Michael Foggs, practicing

1 allergist and chief of allergy and immunology for  
2 Advocate Health Care, a large managed care  
3 organization located in Chicago, Illinois.

4 DR. BUENCONSEJO: I'm Joan Buenconsejo,  
5 statistical team leader, supporting the Division of  
6 Pulmonary, Allergy and Rheumatology Products.

7 DR. PORTER: Hello. I'm Brian Porter, a  
8 medical officer in the Division of Pulmonary,  
9 Allergy and Rheumatology Products.

10 DR. LIMB: Susan Limb. I'm the clinical  
11 team leader at FDA.

12 DR. CHOWDHURY: I'm Badrul Chowdhury. I'm  
13 the division director, Division of Pulmonary,  
14 Allergy and Rheumatology Products.

15 DR. ROSEBRAUGH: Curt Rosebraugh, director  
16 of Office of Drug Evaluation II.

17 DR. KRISHNAN: Great. Thank you very much.  
18 I'd like to make some opening remarks.

19 For topics such as those being discussed at  
20 today's meeting, there are often a variety of  
21 opinions, some of which are quite strongly held.  
22 Our goal is that today's meeting will be a fair and

1 open forum for discussion of these issues and that  
2 individuals can express their views without  
3 interruption. Thus as a gentle reminder,  
4 individuals will be allowed to speak into the  
5 record only if recognized by the Chair. We look  
6 forward to a productive meeting today.

7 In the spirit of the Federal Advisory  
8 Committee Act and the Government in the Sunshine  
9 Act, we ask that the advisory committee members  
10 take care that their conversations about the topic  
11 at hand take place in the open forum of the  
12 meeting. We are aware that members of the media  
13 are anxious to speak with the FDA about these  
14 proceedings. However, FDA will refrain from  
15 discussing the details of this meeting with the  
16 media until its conclusion.

17 I'd like to remind everyone present to  
18 please silence your cell phones and other  
19 electronic devices if you have already not done so.  
20 The committee is reminded to please refrain from  
21 discussing the meeting topic during breaks or  
22 lunch. Thank you.

### **Conflict of Interest Statement**

1  
2 DR. KHUC: The Food and Drug Administration  
3 is convening today's meeting of the Pulmonary-  
4 Allergy Dugs Advisory Committee under the authority  
5 of the Federal Advisory Committee Act of 1972.  
6 With the exception of the industry representative,  
7 all members and temporary voting members of the  
8 committee are special government employees or  
9 regular federal employees from other agencies and  
10 are subject to federal conflict of interest laws  
11 and regulations.

12 The following information on the status of  
13 this committee's compliance with federal ethics and  
14 conflict of interest laws, covered by, but not  
15 limited, to those found at 18 U.S.C. Section 208  
16 and Section 712 of the Federal Food, Drug and  
17 Cosmetic Act, is being provided to participants in  
18 today's meeting and to the public.

19 FDA has determined that members and  
20 temporary voting members of this committee are in  
21 compliance with federal ethics and conflict of  
22 interest laws. Under 18 U.S.C. Section 208,

1 Congress has authorized FDA to grant waivers to  
2 special government employees and regular federal  
3 employees who have potential financial conflicts  
4 when it is determined that the agency's need for a  
5 particular individual's services outweighs his or  
6 her potential financial conflict of interest.

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

13 Related to the discussion of today's  
14 meeting, members and temporary voting members of  
15 this committee have been screened for potential  
16 financial conflicts of interests of their own as  
17 well as those imputed to them, including those of  
18 their spouses or minor children and for purposes of  
19 18 U.S.C. Section 208, their employers. These  
20 interests may include investments, consulting,  
21 expert witness testimony, contracts, grants,  
22 CRADAs, teaching, speaking, writing, patents and

1 royalties and primary employment.

2 Today's agenda involves new drug application  
3 22150, icatibant solution for injection, proposed  
4 trade name Firazyr, Shire Human Genetic Therapies  
5 for the proposed indication of treatment of acute  
6 attacks of hereditary angioedema. This is a  
7 particular matters meeting during which specific  
8 matters related to Shire's Firazyr, icatibant, will  
9 be discussed.

10 Based on the agenda for today's meeting and  
11 all financial interests reported by the committee  
12 members and temporary voting members, no conflict  
13 of interest waivers have been issued in connection  
14 to this meeting. To ensure transparency, we  
15 encourage all standing committee members and  
16 temporary voting members to disclose any public  
17 statements that they've made concerning the product  
18 at issue.

19 With respect to the FDA's invited industry  
20 representative, we would like to disclose that  
21 Dr. Ellen Strahlman is participating in this  
22 meeting as a nonvoting industry representative,

1 acting on behalf of regulated industry.  
2 Dr. Strahlman's role at this meeting is to  
3 represent industry in general and not any  
4 particular company. Dr. Strahlman is an employee  
5 of GlaxoSmithKline.

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

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

17 DR. KRISHNAN: Thank you.

18 We will now proceed with the FDA opening  
19 remarks.

20 **Opening Remarks**

21 DR. CHOWDHURY: Thank you, Dr. Krishnan.

22 On behalf of the FDA and the Division of

1 Pulmonary-Allergy and Rheumatology products, I  
2 welcome you, members of the committee and others on  
3 the advisory panel, representatives of Shire and  
4 the consultants, and members of the audience to  
5 this meeting. We're looking forward to an  
6 interesting and productive meeting.

7 I now turn over the meeting to Dr. Susan  
8 Limb. Dr. Limb will present the objective of this  
9 advisory committee meeting and provide a high-level  
10 summary of the application. Thank you.

11 DR. LIMB: Good morning, honorable  
12 chairperson and members of the committee,  
13 representatives of Shire and other members in the  
14 audience. I welcome you to this meeting on behalf  
15 of the U.S. Food and Drug Administration.

16 In this brief introduction, I'll provide a  
17 high-level summary of the application and present  
18 the questions that you will be discussing and  
19 voting on later today.

20 The objective of today's meeting is to  
21 discuss the new drug application submitted by Shire  
22 Human Genetic Therapies for icatibant for the

1 treatment of acute attacks of hereditary  
2 angioedema.

3 Shire will be presenting an overview of  
4 hereditary angioedema later this morning, so I will  
5 limit myself to a brief description of the disease  
6 here. Hereditary angioedema, or HAE, is a rare  
7 disease characterized by low or absent levels of  
8 functional C1 esterase inhibitor protein.

9 Clinically, HAE is characterized by intermittent,  
10 unpredictable attacks of edema at various parts of  
11 the body such as the upper airways, face,  
12 extremities and the gastrointestinal tract. These  
13 attacks can cause severe pain and are potentially  
14 life-threatening.

15 Treatment options available for HAE can be  
16 divided into therapies for acute attacks and  
17 treatments intended for prophylaxis of acute  
18 attacks. In the United States, androgenic steroids  
19 and C1 inhibitor replacement products are available  
20 for prophylaxis. However, despite prophylaxis,  
21 acute attacks still occur.

22 To address this need, there has been much

1 interest in developing products to treat acute  
2 attacks specifically. Recently, there have been  
3 two products approved in the U.S. for the treatment  
4 of acute attacks. One is a C1 inhibitor  
5 replacement product called Berinert. The second is  
6 Kalbitor, a kallikrein antagonist. Both products  
7 carry a risk of hypersensitivity reactions,  
8 including anaphylaxis and require administration in  
9 a healthcare setting.

10 The focus of today's discussion is  
11 icatibant, a new molecular entity which is proposed  
12 for the treatment of acute HAE attacks. It is a 10  
13 amino acid bradykinin antagonist supplied as a  
14 subcutaneous injection in a prefilled syringe.  
15 Icatibant is proposed for administration as a  
16 single 30-milligram injection by a healthcare  
17 professional or by patient self-administration. In  
18 the event of persistent symptoms or recurrent  
19 symptoms, up to two additional injections may be  
20 administered within a 24-hour period.

21 The company originally submitted this  
22 application to the agency in 2007 for the same dose

1 and indication. This table highlights the major  
2 clinical studies in patients with HAE that were  
3 included in the original submission. In 2007, the  
4 application included the results of a proof of  
5 concept trial and two pivotal efficacy and safety  
6 trials in patients with HAE. These studies were  
7 called FAST-1 and FAST-2. The submission also  
8 included studies to validate the use of a patient-  
9 reported instrument for the primary efficacy  
10 variable.

11 The application was not discussed at an  
12 advisory committee meeting at the time, and we did  
13 not approve the application due to concerns about  
14 the robustness of the efficacy data, which are  
15 discussed in more detail on the next slide.

16 This slide highlights the issues that led to  
17 the not approvable action in 2008. It's worth  
18 noting here that the regulatory requirements for  
19 substantial evidence of efficacy and safety applies  
20 to orphan products intended for rare diseases.  
21 This is the same standard that is expected for  
22 products intended to treat more common conditions.

1           In the case of icatibant, the original  
2 application fell short of this standard. Of the  
3 two main efficacy and safety trials, one trial had  
4 a placebo control while the other trial used an  
5 active comparator. Both trials had the same  
6 primary efficacy endpoint, the time to onset of  
7 symptom relief. The placebo control trial, FAST-1,  
8 did not show a statistically significant difference  
9 between icatibant and placebo for this prespecified  
10 primary endpoint.

11           In contrast, the other trial, FAST-2, did  
12 demonstrate a statistically significant difference  
13 between icatibant and the active comparator,  
14 tranexamic acid. However, tranexamic acid is not  
15 approved for the treatment of HAE in the U.S., and  
16 there is limited data to support the efficacy of  
17 tranexamic acid for the treatment of acute attacks.  
18 The uncertain efficacy of this active comparator  
19 complicated the interpretation of study results,  
20 and the agency was unable to conclude that there  
21 was substantial evidence of efficacy.

22           Subsequently, Shire provided post hoc

1 analysis, using a modified primary endpoint that  
2 you will hear about in detail later today. While  
3 the results of these additional analyses were  
4 supportive, the agency declined to accept these  
5 post hoc results as the basis for approval. The  
6 agency asked that Shire conduct an additional  
7 control trial to confirm efficacy for icatibant.  
8 The agency also asked that Shire provide data to  
9 support patient self-administration as had been  
10 proposed in the original application.

11 In response, Shire conducted an additional  
12 placebo-controlled efficacy and safety trial called  
13 FAST-3 and an open label self-administration trial  
14 to address the issues that were raised during the  
15 first review cycle. This additional information  
16 was included in the complete response that was  
17 submitted in February of this year.

18 In today's meeting, we will be examining the  
19 clinical data in its entirety from both the  
20 original submission and the complete response. The  
21 details of the clinical program will be provided in  
22 the presentations to follow. As you can see on the

1 agenda, we will start with presentations from the  
2 company followed by presentations from the FDA.

3 As you hear the presentations, there are  
4 three major issues that I would like you to  
5 consider. The first is the robustness of the  
6 efficacy data for icatibant in the proposed  
7 indication, the second is the adequacy of the  
8 safety data, and the third is the issue of self-  
9 administration and whether self-administration  
10 raises any particular issues in terms of safety or  
11 efficacy.

12 These three major issues are the basis for  
13 the questions that you will discuss and vote on  
14 later today. There are a total of five questions.  
15 Two of the questions are intended for our  
16 discussion, while the remaining three will require  
17 voting.

18 I will now go over these questions. In the  
19 interest of time, I won't be reading them verbatim,  
20 but you may refer to the written materials for the  
21 exact wording.

22 Question 1 is actually not a question but a

1 request to discuss the efficacy and safety data  
2 presented today.

3 Question 2 is the follow-up voting question  
4 on efficacy. We will ask you to vote and to  
5 provide a rationale for your vote and any  
6 additional comments that you might have.

7 Question 3 is the voting question on safety.  
8 As for Question 2, you will vote and provide a  
9 rationale for your vote.

10 Question 4 is the final voting question.  
11 This question pertains to the overall risk-benefit  
12 profile for icatibant and your approvability  
13 recommendation for this drug to the agency.

14 Question 5 is the last question. It's a  
15 nonvoting question where we will ask you to discuss  
16 the proposed self-administration of icatibant and  
17 the implications this might have on safety and  
18 efficacy, if any.

19 Before closing, I would like to return to  
20 the stated objective for this meeting and make some  
21 general comments about the advisory committee  
22 process. In today's meeting, we will discuss the

1 clinical efficacy and safety data for icatibant.  
2 Various other issues, such as drug product quality,  
3 manufacturing and controls, are also considered in  
4 the review of the application. These other aspects  
5 of the application, however, will not be discussed  
6 today.

7 In addition, please know that the feedback  
8 that you provide today is advisory but not  
9 decisional. The agency utilizes committee meetings  
10 as an opportunity to conduct public hearings on  
11 matters of importance and as an opportunity to  
12 solicit feedback and recommendations. The agency,  
13 however, has discretion concerning any actions and  
14 policies that result from the input provided by you  
15 today. Nevertheless, your opinion and comments are  
16 important and factor prominently in our decision  
17 making.

18 In summary, we look forward to an  
19 interesting meeting and thank the members of the  
20 committee for their time and effort. Your  
21 participation in this important public service  
22 reflects your dedication to the practice of

1 medicine as well as public health.

2 At this point, I will now turn the meeting  
3 back to Dr. Krishnan. Thank you.

4 DR. KRISHNAN: Great. Thank you very much,  
5 Dr. Limb.

6 Both the Food and Drug Administration and  
7 the public believe in a transparent process for  
8 information gathering and decision making. To  
9 ensure such transparency at the advisory committee,  
10 the FDA believes that it's important to understand  
11 the context of an individual's presentation. For  
12 this reason, FDA encourages all participants,  
13 including the sponsor's nonemployee presenters, to  
14 advise the committee of any financial relationship  
15 that they may have with the firm at issue such as  
16 consulting fees, travel expenses, honoraria and  
17 interests in the sponsor, including equity interest  
18 and those based upon the outcome of the meeting.  
19 Likewise, FDA encourages you at the beginning of  
20 your presentation to advise the committee if you do  
21 not have any such financial relationships. If you  
22 choose not to address this issue of financial

1 relationships at the beginning of your  
2 presentation, it will not preclude from speaking.

3 We will now proceed with the sponsor's  
4 presentations.

5 **Sponsor Presentation - Philip Vickers**

6 DR. VICKERS: Thank you, Dr. Krishnan, and  
7 good morning to everybody.

8 My name is Phil Vickers. I'm senior vice  
9 president and head of research and development at  
10 Shire Human Genetic Therapies. I'd like to thank  
11 the members of the committee and the FDA for the  
12 opportunity to speak to you this morning and to the  
13 patients and advocates who have joined us to  
14 represent the views of the hereditary angioedema or  
15 HAE community. We at Shire HGT are aiming to meet  
16 the needs of this community.

17 As you'll hear during our -- we are here  
18 today seeking the committee's endorsement for the  
19 indication you see here. Firazyr, icatibant, 13  
20 mgs subcutaneous injection is indicated for the  
21 treatment of acute attacks of hereditary angioedema  
22 in adults.

1           As you'll hear during our presentation  
2 today, HAE is a rare and debilitating disease.  
3 There are less than 30,000 HAE patients in the  
4 U.S.A. Because of this low incidence, the FDA has  
5 designated HAE as an orphan indication. Icatibant  
6 was granted orphan status in November 2003 and was  
7 granted fast track status by the FDA in December  
8 2004. If approved, we believe that icatibant will  
9 provide an important new therapy for patients with  
10 HAE and their families.

11           Here is the agenda for our presentation. I  
12 will provide a brief overview of icatibant,  
13 including its development history. Dr. William  
14 Lumry, an investigator in our definitive phase 3  
15 clinical trial, FAST-3, will review the unmet  
16 medical need for HAE, including its natural  
17 history, the current treatment strategies for HAE  
18 and the recommendations from international  
19 treatment guidelines for enhancement of these  
20 treatment strategies. Dr. Sue Cammarata, vice  
21 president of clinical research at Shire HGT, will  
22 review the efficacy and safety data from our

1        icatibant trials. Dr. Marc Riedl, also an  
2        investigator in our FAST-3 clinical trial, will  
3        then share his perspective about the icatibant data  
4        and whether they address the unmet medical needs  
5        that Dr. Lumry will have described. Dr. Cammarata  
6        will then return to summarize the icatibant  
7        benefit-risk profile and offer our conclusions.  
8        She will then lead the team in responding to  
9        questions from the committee.

10                Icatibant is a first in class, potent and  
11        selective antagonist of the bradykinin B2 receptor.  
12        As will be shown by Dr. Lumry, bradykinin induces  
13        the hallmark symptom of HAE, edema, through its  
14        interaction with the B2 receptor. There is a  
15        strong rationale that a specific antagonist of this  
16        receptor will be effective in the treatment of  
17        acute attacks of HAE. To facilitate patient  
18        access, icatibant was formulated for subcutaneous  
19        injection using a prefilled syringe that can be  
20        stored at room temperature.

21                Icatibant was discovered and initially  
22        developed by Hoechst Marion Roussel. Hoechst

1 Marion Roussel sold the rights for icatibant to  
2 Jerini AG who conducted the initial phase 3 trials,  
3 FAST-1 and FAST-2, and submitted an NDA in October  
4 2007. The FDA concluded in April of 2008 that  
5 these trials were insufficient to establish  
6 efficacy and safety and that they were uncertain  
7 about the validity of the primary endpoint used in  
8 those trials. The FDA requested a third phase 3  
9 trial be conducted to definitively establish  
10 icatibant efficacy and safety.

11 Subsequent to the FDA's decision, Shire  
12 acquired Jerini AG. Following discussions with the  
13 FDA, Shire conducted the definitive phase 3 trial,  
14 FAST-3, and submitted a response to the FDA in  
15 February 2011. The European Medicines Agency  
16 approved icatibant for HAE in July 2008 and  
17 subsequently approved icatibant for patient self-  
18 administration in February 2011. Based on the  
19 totality of the data we will present today, we  
20 believe that icatibant will make an important  
21 contribution to the treatment of HAE.

22 I'd like to now introduce Dr. William Lumry.

1                   **Sponsor Presentation - William Lumry**

2                   DR. LUMRY: Thank you, Dr. Vickers.

3                   My name is William Lumry. I'm a clinical  
4 professor at the University of Texas Southwestern  
5 Medical School and medical director of the Allergy  
6 and Asthma Research Center in Dallas, Texas. I  
7 appreciate the opportunity provided by the  
8 committee and Shire to speak with you today about  
9 hereditary angioedema, a rare, disabling and  
10 debilitating disease that is often under-recognized  
11 and often inadequately treated even after it has  
12 been diagnosed.

13                  For disclosure, I would like to note that I  
14 am investigator, scientific advisor and consultant  
15 for Shire HGT. My interest in hereditary  
16 angioedema began during my clinical research  
17 fellowship at Scripps Clinic in 1980. I currently  
18 care for 65 individuals with this rare disorder.

19                  Hereditary angioedema is a rare disorder  
20 that represents only 2 percent of all cases of  
21 angioedema. Global prevalence estimates range  
22 between one in 10,000 and one in 50,000. The

1 number of U.S. patients is estimated to be between  
2 6,000 and 30,000 individuals.

3 Hereditary angioedema is a genetic disorder  
4 of autosomal dominant transmission, variable  
5 penetrants and variable expression. The genetic  
6 mutations result in either a deficiency or a  
7 dysfunction of C1 esterase inhibitor. C1 inhibitor  
8 regulates complement, coagulation, fibrinolytic and  
9 kinin pathways. C1 inhibitor is the most important  
10 inhibitor of plasma kallikrein which liberates  
11 bradykinin from high molecular weight kininogen.  
12 Bradykinin acting through the bradykinin 2 receptor  
13 on vascular epithelial cells causes vasodilation,  
14 opening of endothelial junctions, and serum  
15 leakage, resulting in localized swelling.

16 Let's look at the pathway involved in the  
17 edema formation in hereditary angioedema. This  
18 cartoon shows you the contact or kinin pathway.  
19 When a negatively-charged surface is exposed,  
20 pre-kallikrein and Factor 12 are activated.  
21 Activated Factor 12 acts on pre-kallikrein to  
22 produce kallikrein, which then liberates bradykinin

1 from high molecular weight kininogen. C1 inhibitor  
2 regulates production of bradykinin by blocking the  
3 effects of Factor 12-A and kallikrein on their  
4 substrates.

5 In this next slide, we see what happens when  
6 C1 inhibitor is deficient. The pathway once  
7 activated runs uncontrolled, resulting in excessive  
8 amounts of kallikrein being produced and large  
9 amounts of bradykinin being liberated. The  
10 bradykinin acts on the bradykinin 2 receptors,  
11 causing the blood vessel to dilate, become leaky  
12 and angioedema is the result.

13 HAE presents as recurring and unpredictable  
14 episodes of swelling. A swelling attack may occur  
15 in peripheral or central cutaneous tissues such as  
16 the hands, feet, face or genitalia. The mucosa of  
17 the lips, tongue, larynx and abdomen are also  
18 commonly swelling. These swelling attacks can be  
19 uncomfortable and disruptive at best or severely  
20 painful, disabling and potentially life-threatening  
21 at worst.

22 Abdominal attacks may present without

1 visible peripheral edema, and abdominal attack  
2 symptoms may include colicky pain, nausea,  
3 vomiting. Third spacing of edema, fluid and  
4 dehydration associated with the vomiting may lead  
5 to hemoconcentration and a relative leukocytosis.  
6 Abdominal attacks can mimic a bowel obstruction or  
7 surgical abdomen and may be treated inappropriately  
8 with surgical intervention.

9 Laryngeal attacks present as airway  
10 constriction or blockage. They can occur as a  
11 progression of mouth, tongue and pharyngeal  
12 swelling. Patients with an impending laryngeal  
13 swelling attack may complain of dysphasia, voice  
14 change, throat tightness and stridor. Although  
15 laryngeal attacks represent only 2 percent of all  
16 HAE attacks, they are life-threatening. Fifty  
17 percent of HAE patients will experience a laryngeal  
18 attack sometime in their lifetime. Laryngeal  
19 attacks, if not treated, are fatal 30 percent of  
20 the time.

21 During an HAE attack, tissue levels of  
22 bradykinin rise rapidly. Edema develops gradually

1 over 2 to 24 hours unless treated, and then will  
2 resolve spontaneously in two to five days as edema  
3 fluid is resorbed. Attacks may begin at one  
4 location and move to another. An individual HAE  
5 patient may experience more than one attack a week  
6 to less than one attack per year. These attacks  
7 are unpredictable, disruptive and often disabling.

8 A variety of triggers have been observed,  
9 although attacks may occur spontaneously. These  
10 triggers include psychological stress; localized  
11 trauma, including medical and dental and surgical  
12 procedures; febrile illness; menses and pregnancy;  
13 as well as treatment with ACE inhibitor which block  
14 the metabolism of bradykinin and estrogens which  
15 may decrease the production of C1 inhibitor.

16 With or without an identified trigger, HAE  
17 patients understand their condition and themselves.  
18 Patients, as you will hear during the open public  
19 forum, are aware of the signs and symptoms of the  
20 swelling attack and often can predict when one is  
21 going to occur.

22 These pictures are representative of some of

1 the types of HAE attacks. On your left are  
2 pictures of a massively swollen hand, face and  
3 lips. In the upper right frame is a swollen ileum  
4 with blockage of the lumen as seen through a  
5 colonoscope. Below that is a barium study showing  
6 marked edema of the bowel wall, thumbprinting along  
7 the villi, and bowel obstruction blocking barium  
8 flow.

9 This is one of my patients who presented to  
10 the emergency room with difficulty swallowing. She  
11 was drooling and unable to speak. This lateral  
12 soft tissue film shows straightening of her  
13 cervical spine and massive swelling of the  
14 posterior pharynx and epiglottis with extreme  
15 narrowing of her airway. She was treated with C1  
16 inhibitor concentrate and recovered uneventfully.  
17 This picture on your right was taken three weeks  
18 after the attack, showing the normal anatomy of her  
19 upper airway.

20 HAE attacks can have a profound impact on  
21 patients' lives. In this survey, 457 HAE patients  
22 were asked to report the impact of their most

1 recent HAE attack. On average, 50 percent of  
2 patients missed work, school, or leisure time as a  
3 result of the attack. Patients also reported  
4 missed educational and career opportunities,  
5 depression, and poor quality of life.

6 Patients and their treating physicians want  
7 a treatment that provides rapid onset of symptom  
8 relief, decreases in time of complete resolution of  
9 symptoms, and allows for a quick return to normal  
10 life, daily activities.

11 Treatment for hereditary angioedema in the  
12 United States and worldwide is evolving as new  
13 therapeutic agents and strategies become available.  
14 Currently, there are no U.S.-specific guidelines  
15 for treating HAE. International and Canadian  
16 treatment guidelines based on expert consensus were  
17 published in the past two years and have guided our  
18 treatment as new therapies have been approved.  
19 These treatment guidelines address both pre-  
20 procedural and chronic prophylactic treatment as  
21 well as attacks. Dr. Riedl will discuss the  
22 specific treatment recommendations in his

1 presentation.

2 HAE experts throughout the world agree that  
3 access to a safe and effective therapy. Early  
4 intervention and self-administration are features  
5 of a desirable acute attack treatment plan and  
6 should decrease the burden of this disorder on  
7 patients.

8 While there is broad agreement on the  
9 benefit of early administration, there is limited  
10 controlled clinical data confirming this  
11 expectation. The controlled clinical trials have  
12 focused on demonstrating only efficacy and safety  
13 of the treatment provided.

14 Studies demonstrating the benefit of early  
15 intervention have used C1 inhibitor concentrate to  
16 treat attacks. The results, however, should be  
17 applicable to all products that disrupt bradykinin-  
18 mediated swelling. When attacks were treated  
19 early, they were less severe and began to subside  
20 within one hour. Conversely, delayed treatment was  
21 shown to prolong attack duration. Anecdotally,  
22 these results agree with the feedback I've gotten

1 from my patients.

2 Self-administration benefit was demonstrated  
3 in a trial by Levi, et al., published in 2006.  
4 This trial included 31 patients who self-  
5 administered C1 inhibitor to treat their angioedema  
6 attacks over a one- to five-year period. The time  
7 between onset of acute attack and the self-  
8 administration of C1 inhibitor was 1.4 hours  
9 compared to 3.4 hours when the treatment was  
10 administered by a healthcare professional.

11 As shown in these graphs on the left, self-  
12 administration led to quicker initiation of symptom  
13 relief with onset averaging at one-half hour versus  
14 3 hours when treatment was provided in hospital.  
15 More importantly, self-administration led to  
16 complete resolution of symptoms within 6 hours  
17 compared to 14 hours for treatments provided by a  
18 healthcare provider.

19 These results were recently confirmed by  
20 Zuraw, et al., in an observational study in 39 HAE  
21 patients who self-administered C1 inhibitor. This  
22 study has been accepted for publication.

1           Based on this commonly accepted goal of  
2 early intervention and supporting data, experts and  
3 the guidelines support the concept that self-  
4 administration and on-demand therapy will  
5 accelerate the time to intervention. But can self-  
6 administration decrease the time to treatment and  
7 resolution of attacks? Experts like myself,  
8 Dr. Riedl, and Dr. Marcus Maurer believe it can.

9           So what is the situation today and how does  
10 that impact the patient during an HAE attack?  
11 Treatment of HAE attacks are usually provided by  
12 healthcare professionals. Neither of the two  
13 available treatments in the United States for acute  
14 attack treatment is approved for self-  
15 administration.

16           Unfortunately, many physicians are  
17 unfamiliar with hereditary angioedema and do not  
18 know how to diagnose or treat an attack. This can  
19 lead to misdiagnosis as a histamine-mediate  
20 allergic reaction or an acute abdominal event.  
21 This in turn may lead to the administration of  
22 ineffective treatment, including antihistamines,

1 epinephrine and steroids, or unnecessary  
2 exploratory abdominal surgery.

3 In most cases, unless the patients can  
4 access their HAE treatment specialist, they will  
5 likely have delayed intervention in the emergency  
6 department due to triage procedures, and further  
7 delay may occur when hospital staff request and  
8 complete testing to confirm the diagnosis.

9 Even when an experienced HAE patient, who  
10 knows their condition well, has information about  
11 their disease and has medication to treat the  
12 attack in their possession, presents to an  
13 emergency department, treatment is often delayed.  
14 The provided medication is often not accepted or  
15 administered secondary to hospital policies against  
16 using patient-supplied medications. As a result,  
17 both HAE patients and their physicians seek ways to  
18 accelerate time to onset of symptom relief and time  
19 to complete resolution. Most of these barriers to  
20 early and effective treatment can be circumvented  
21 by availability of a therapy that is readily  
22 accessible and can be self-administered.

1           In summary, HAE attacks are caused by  
2           unregulated bradykinin production. Patients suffer  
3           debilitating edema, pain, and, unfortunately,  
4           occasionally death. The patients' quality of life  
5           is decreased at work, school, and at home.  
6           Fortunately, effective treatments have been  
7           approved in the past few years, but currently they  
8           are not readily accessible. The available  
9           guidelines, treating physicians, patients and  
10          patients' advocates agree, we need an effective and  
11          safe treatment for immediate use, a treatment that  
12          can be administered by the patient or a caregiver  
13          outside of a medical care setting.

14                 Treating physicians and patients are seeking  
15          safe treatments that provide both prompt onset of  
16          relief and shortened duration of attack, the two  
17          major goals of HAE guidelines for management of  
18          acute attacks. Having a treatment with an  
19          acceptable risk-benefit ratio that is readily  
20          accessible and can be administered by the patient  
21          or a caregiver at the onset of an attack will be a  
22          great move forward toward achieving this goal.

1           Thank you for your attention. At this time,  
2 I would like to introduce Dr. Sue Cammarata of  
3 Shire HGT who will present the clinical study data.

4           **Sponsor Presentation - Sue Cammarata**

5           DR. CAMMARATA: Thank you, Dr. Lumry. And  
6 thank you and good morning. I'm Sue Cammarata.  
7 I'm the vice president of clinical research at  
8 Shire HGT.

9           Today I'll be presenting an overview of the  
10 icatibant development program, beginning with the  
11 information on our early development program. I'll  
12 then move to the phase 3 efficacy data and study  
13 design, and I'll begin with the definitive trial,  
14 FAST-3, as well as the supportive trials, FAST-1  
15 and FAST-2. As part of the discussion, I'll  
16 provide data on laryngeal attack efficacy as well  
17 as efficacy with repeat attacks.

18           I'll then go on to the icatibant safety  
19 information, looking at the first attack compared  
20 to control data, as well as safety from icatibant  
21 use for repeat attacks. Finally, I'll provide the  
22 safety data from our open label self-administration

1 study that's known as the EASSI trial. All the  
2 data discussed today is also provided in your  
3 briefing book.

4 This is the largest database submitted to  
5 the FDA for review and approval in this orphan  
6 indication for the treatment of acute attacks of  
7 HAE. Collectively, we have data for 236 patients  
8 who received icatibant 30 milligrams in the phase 2  
9 and the phase 3 trials and the subsequent open  
10 label extensions. This included 1,055 acute HAE  
11 attacks as well as 60 patients who suffered from  
12 acute laryngeal attacks. We also have data on  
13 225 patients with one or more attacks of HAE  
14 treated with icatibant, including 38 patients who  
15 were treated for more than five attacks.

16 I'd now like to quickly review the phase 1  
17 and the phase 2 studies that supported the phase 3  
18 program.

19 Clinical development of icatibant was  
20 initiated in the early 1990s. The phase 1 and the  
21 phase 2 studies to support the use of icatibant in  
22 HAE are listed here. The highlighted studies

1 helped us to select 30 milligrams as the preferred  
2 sub-Q dose. These were Studies 1001, 1102 and  
3 2101. I won't be reviewing these studies in detail  
4 today since they're summarized in your briefing  
5 book.

6 The efficacy and safety of icatibant for  
7 treatment of acute attacks of HAE have been  
8 investigated in three controlled phase 3 trials.  
9 I'll be referring to these today as the FAST-1, the  
10 FAST-2, and the FAST-3 trials. FAST-3 is our  
11 definitive trial to demonstrate efficacy and safety  
12 of icatibant for the treatment of acute attacks.  
13 FAST-3 was completed by Shire after discussion with  
14 the FDA and was included in our complete response.

15 FAST-1 and FAST-2 provide further evidence  
16 of efficacy and safety. They were completed by  
17 Jerini and included in our original submission.

18 The three controlled phase 3 studies were  
19 very similar in design. All three studies had a  
20 controlled phase in which the subjects had one  
21 moderate or severe cutaneous or abdominal first  
22 attack, and they were assigned randomly to receive

1       blinded treatment with either icatibant or placebo  
2       in FAST-1 and FAST-3 or tranexamic acid in FAST-2.  
3       The laryngeal attack patients were treated in an  
4       open label fashion. But in FAST-3, we attempted to  
5       randomize mild to moderate laryngeal attacks to  
6       icatibant or placebo.

7               All three trials had an open label extension  
8       phase in which patients could elect to continue,  
9       and they would participate for subsequent attacks.  
10       The open label extension for FAST-3 is ongoing, and  
11       96 subjects in FAST-3 actively remain in the  
12       extension of that trial.

13               Shire also conducted an open label phase 3B  
14       study, the EASSI trial, to evaluate self-  
15       administered icatibant. One hundred fifty-one  
16       patients were consented to participate, and an  
17       interim analysis of the data from 56 subjects was  
18       submitted to the FDA in February. The trial is  
19       ongoing, and the final study results are going to  
20       be reported in September.

21               So let me describe the evaluations that we  
22       used in these trials. These studies were designed

1 to capture the symptoms of an acute HAE attack.  
2 Given the variability of HAE attacks and the  
3 uncertainty for actual enrollment, a number of  
4 patients were screened for the history of HAE  
5 attacks, and they were prequalified for enrollment.  
6 When an attack began, the prescreened patient would  
7 go to the clinic and be randomized to receive  
8 either icatibant or the comparator once their  
9 primary symptom became moderate or severe. And the  
10 scoring at enrollment then became their baseline  
11 score.

12           Enrolled patients received a sub-Q injection  
13 of either icatibant or the comparator. Patients  
14 then entered a 48-hour attack assessment phase  
15 where they were systematically evaluated at  
16 multiple time points. The first measure occurred  
17 one hour after the injection. Further assessments  
18 were taken every half hour until four hours after  
19 the injection. Measures were then taken every hour  
20 through 12 hours and again at 24 and 48 hours. The  
21 patients were most intensively assessed over that  
22 two-day period.

1           If patients had persistent symptoms, they  
2 had intermittent evaluations through day 5. And  
3 thereafter, patients were followed for adverse  
4 events through 14 days, and they had periodic  
5 ad hoc adverse event reporting beyond that period.  
6 So I'd like to review the measures, the symptoms  
7 and the endpoints that were used in the phase 3  
8 trials.

9           Now, assessments in HAE trials historically  
10 rely on patient-reported outcomes on symptoms such  
11 as pain, swelling, difficulty swallowing, and the  
12 icatibant patient-reported outcomes were validated  
13 as per the FDA guidance. For the primary endpoint,  
14 a visual analog scale, a VAS or V-A-S, was used. A  
15 VAS is a standardized validated measure for  
16 patient-reported symptom severity. VAS scoring has  
17 been employed frequently by sponsors and the FDA to  
18 support efficacy and to also support indications  
19 for approval such as pain indications.

20           The VAS displays a 100-millimeter horizontal  
21 line to the patient with extremes values ranging  
22 from no symptoms on one end to the worst possible

1 symptoms on the other end. The patient then draws  
2 a vertical line at a point along the scale that  
3 shows their perception of the symptom at that  
4 moment in time. The VAS measures the severity for  
5 each symptom of attack at pretreatment, and then  
6 it's done at various time points throughout the  
7 treatment period.

8 The patient's use of VAS has been documented  
9 to reliably represent the individual patient's  
10 perception of a given symptom in time and over  
11 time. Historically, changes in VAS of 10 to 20  
12 millimeters represent a clinically meaningful  
13 change in the perception of pain.

14 To successfully use those patient-reported  
15 outcomes, you have to evaluate clinically-relevant  
16 symptoms. The phase 3 clinical trials explicitly  
17 assessed important HAE symptoms using a visual  
18 analog scale for the primary endpoint. We  
19 collected six individual symptoms with single VAS  
20 scores across the three studies, including skin  
21 swelling, skin pain, abdominal pain, difficulty  
22 swallowing, voice change and nausea.

1           For FAST-3, we prospectively declared that  
2 we would use a composite score that we discussed  
3 with the FDA for our primary endpoint known as the  
4 VAS-3. The symptoms that comprise the VAS-3, skin  
5 pain, skin swelling and abdominal pain, are by far  
6 the most reported and significant symptoms for HAE  
7 patients for both abdominal and cutaneous attacks.  
8 This measure reflects the range of the most  
9 important symptoms that patient experience.

10           The sum of the three single VAS measures was  
11 averaged to generate the composite score. For  
12 FAST-1 and FAST-2, a VAS-3 was calculated post hoc.  
13 This was based on the prospectively collected  
14 single VAS data that allowed us to do comparisons.  
15 And we also wanted to understand efficacy for  
16 laryngeal attacks. So two more symptoms were  
17 added, the difficulty swallowing and voice change.  
18 This was included in VAS-3 to calculate the  
19 composite VAS laryngeal attacks which is called the  
20 VAS-5 since it has five symptoms. These two  
21 laryngeal symptoms are the most common early  
22 indicators of laryngeal involvement. The final

1       scoring was based on an average of those five  
2       single VAS score symptoms.

3               In addition, we also wanted to broadly  
4       capture the many HAE symptoms that have been  
5       identified and validated to assess efficacy in HAE.  
6       So in contrast to the VAS, these were also captured  
7       using an individual symptom score using either a  
8       five-point or a seven-point scale. In most cases,  
9       these were rated by both the patient and the  
10       investigator. However, there are a few exceptions,  
11       as noted in your briefing book, and this is  
12       primarily linked to the ability of the investigator  
13       and the patient to accurately assess them.

14               We captured also global assessment scores  
15       for cutaneous abdominal laryngeal symptoms as  
16       scored by the investigator. So within the phase 3  
17       studies, we evaluated those symptoms that are most  
18       important to HAE patients. We used measures, both  
19       VAS and symptom scores, that reflect clinically  
20       meaningful changes.

21               Now, the VAS and the symptom scores were  
22       used to document changes in symptoms over time

1 after the injection. So we have these time to  
2 endpoints that follow the time course of an acute  
3 HAE attack, from the beginning of the attack to  
4 treatment administration, from a drug  
5 administration to the time of initial symptom  
6 improvement, when the patient first noticed any  
7 improvement. We also looked at the onset of  
8 symptom relief, which was a stringently protocol-  
9 defined endpoint. And ultimately, we also looked  
10 to what we call almost complete symptom relief or  
11 resolution of the attack where all the VAS scores  
12 had to be less than 10 millimeters.

13 The key endpoints were focused on the time  
14 to onset of symptom relief, either based on the  
15 single symptom, the single VAS or positive  
16 symptoms, this composite VAS. Achieving this  
17 endpoint is based on the earliest of three  
18 consecutive measurements in which there was the  
19 target reduction in symptom severity.

20 These endpoints and points best demonstrate  
21 the treatment response that a patient wants. "When  
22 am I going to get better?" We measured the time to

1 initial symptom improvement and the time to the  
2 onset of symptom relief, either by the single or  
3 composite VAS. Patients also want to know when  
4 will this pretty much be over. We measured time to  
5 almost complete symptom relief.

6 So as I've outlined, we've measured  
7 clinically-relevant symptoms using validated  
8 measures with clinically-relevant endpoints which  
9 marked the important milestones in a patient's  
10 response during an attack.

11 The time to symptom relief, based on a  
12 composite VAS-3, was the primary endpoint in our  
13 definitive trial, FAST-3. The composite VAS-3 best  
14 represents the patient's response to treatment  
15 since it incorporates primary symptoms that are  
16 important to patients. A change of just  
17 5 millimeters in the composite VAS differentiated  
18 improved from unimproved patients.

19 Based on the prospectively collected single  
20 VAS scores, we were also able to calculate a VAS-3  
21 for the FAST-1 and the FAST-2 trials to allow  
22 cross-study comparisons. The scores from the

1 single VAS measurements that were used for the  
2 primary endpoints in FAST-1 and FAST-2 and the  
3 secondary endpoint in FAST-3 also allowed further  
4 cross-study comparisons.

5 Other endpoints that we'll present today  
6 include time to initial symptom improvement, mean  
7 composite VAS over time, time to almost complete  
8 symptom relief. There are numerous other secondary  
9 endpoints collected and are included in your  
10 briefing book, but it's not our intention to review  
11 all of those in this presentation.

12 In the presentation for the phase 3 results  
13 today, I'll be discussing the results in this  
14 order. First, primary results of the double-blind  
15 dosing of the abdominal and cutaneous attacks for  
16 the non-laryngeal patients in FAST-3 followed by  
17 FAST-1 and FAST-2. These each represent the  
18 populations used for the primary endpoints. Then  
19 I'll review the pooled FAST trial results for the  
20 patients who decided to move into the open label  
21 extension for repeat treatment of subsequent  
22 attacks. And finally, I'll present the pooled

1 results for all patients in the FAST trials and the  
2 extensions that presented with laryngeal attacks.

3 So let's begin with FAST-3 looking at the  
4 data for our non-laryngeal patients. After  
5 consultation with the FDA, Shire initiated the  
6 FAST-3 trial. The design of all the FAST trials  
7 were similar, particularly the randomization of  
8 non-laryngeal attacks and the option for the open  
9 label extension. In the definitive FAST-3 trial,  
10 patients were prescreened and presented to the  
11 study site upon HAE attack, and FAST-3 enrolled  
12 98 patients.

13 In the controlled phase, a total of  
14 88 patients presenting with an eligible abdominal  
15 or cutaneous first attack were randomized to  
16 blinded treatment with icatibant or placebo. For  
17 patients with primarily laryngeal symptoms, an  
18 amendment of the FAST-3 protocol allowed patients  
19 with mild to moderate laryngeal symptoms to be  
20 randomly assigned to blinded treatment with either  
21 icatibant or placebo, but all patients with severe  
22 laryngeal attacks received open label icatibant.

1           After this initial attack on study, patients  
2 could elect to enroll in the open label extension  
3 to have subsequent HAE attacks treated with  
4 icatibant. This allowed us to collect data on  
5 multiple attacks to demonstrate safety and  
6 continued effectiveness of icatibant in HAE attacks  
7 over time. Ninety-six patients rolled over into  
8 the extension, and 58 patients were treated in the  
9 extension by the time of the data cut. And the  
10 open label portion of this study is still ongoing.

11           Forty-three subjects with cutaneous or  
12 abdominal attacks were randomized to icatibant.  
13 Forty-five patients randomized to placebo. No  
14 patients in the icatibant group discontinued the  
15 48-hour controlled portion of the study. There was  
16 one death in the placebo group which was due to an  
17 MI.

18           The icatibant and placebo groups were  
19 similar for age, sex and weight. Average age was  
20 in the mid-30s, and the majority of patients in  
21 both treatment groups were white.

22           So what was the outcome for these patients

1 with a single dose of icatibant in an HAE attack?  
2 On the following slide, we have the key results  
3 form that study.

4 Now, we've used Kaplan-Meier curves to show  
5 the progress of patients as they respond to  
6 treatment over time. When displayed this way, we  
7 actually allow you to see the response of every  
8 patient in the trial. The Y axis shows the  
9 percentage of patients who've not yet met the  
10 target endpoint. So when you move from left to  
11 right, we're showing you each patient as they  
12 respond to therapy and hit that target endpoint.

13 This Kaplan-Meier curve from the FAST-3  
14 trial shows the primary endpoint of time to onset  
15 of symptom relief based on that composite VAS  
16 score, the VAS-3. It shows a rapid drop in the  
17 graph for the icatibant-treated patients as each  
18 patient reaches the endpoint. Icatibant was  
19 significantly better than placebo in the treatment  
20 of HAE attacks.

21 In the analyses of these cutaneous and  
22 abdominal attacks, icatibant patients had onset of

1 symptom relief based on the composite VAS-3 in a  
2 median two hours. This was compared to placebo  
3 patients where relief was not seen for a median of  
4 19.8 hours.

5 Next, if you look at the Kaplan-Meier curve  
6 for time to onset of symptom relief based on the  
7 primary single VAS for each patient, we again show  
8 you the response of each patient in the trial.  
9 Icatibant also significantly decreased the time to  
10 onset of primary symptom relief which was based on  
11 that single primary VAS and a median of 1.5 hours  
12 when compared to placebo which had a median 18.5  
13 hours. And since we followed the patients through  
14 their recovery, we also assessed the time to almost  
15 complete symptom relief where all VAS scores were  
16 less than 10 millimeters.

17 Icatibant accelerated the resolution of  
18 attacks as measured by almost complete symptom  
19 relief at a median of 8 hours compared to placebo's  
20 median of 36 hours as shown in this Kaplan-Meier  
21 where we're now extended the X axis out to 120  
22 hours. The faster time to no resolution of attacks

1 reduced the amount of time that patients  
2 experienced the debilitating symptoms of HAE.

3 Now, that we've looked at the most recently  
4 completed definitive trial, let's turn our  
5 attention to the original first two FAST trials,  
6 which we consider supportive trials.

7 FAST-1 and FAST-2 are similar in design.  
8 Patients were prescreened and presented to the  
9 study site upon attack. With cutaneous or  
10 abdominal attacks, patients were randomized to  
11 double-blind treatment, icatibant versus placebo in  
12 FAST-1, icatibant and tranexamic acid in FAST-2.  
13 One hundred and twenty-eight patients entered these  
14 arms with 61 treated with icatibant, 29 with  
15 placebo, and 38 with tranexamic acid.

16 In FAST-1 and FAST-2, patients presenting  
17 with an laryngeal attack were treated with open  
18 label icatibant. There were 13 laryngeal patients  
19 in these studies.

20 After the controlled portion was enrolled,  
21 Jerini allowed 28 previously screened but not  
22 randomized patients to enter an open label arm.

1 After this first attack was treated, patients then  
2 could elect to enroll into the open label portion  
3 to have future attacks treated with icatibant, and  
4 this again allowed us to collect data on the  
5 effectiveness of icatibant over time for repeat  
6 attacks.

7 Sixty-one patients with cutaneous or  
8 abdominal attacks were randomized to icatibant in  
9 these two trials, 29 randomized to placebo and  
10 38 patients received tranexamic acid. No patients  
11 in the icatibant group discontinued the control  
12 portion of the studies.

13 So let's turn to the results from these two  
14 earlier phase 3 studies, and I'll be showing you  
15 the same endpoints I've just shown you for the  
16 FAST-3 trial.

17 In FAST-1, icatibant was effective in the  
18 treatment of acute HAE with a primary endpoint,  
19 showing a consistent onset of primary symptom  
20 relief of 2.3 hours compared to the median time of  
21 onset of 5 hours with placebo. As discussed in the  
22 briefing book, the placebo effect was better than

1        seen in other trials, and FAST-1 did not meet its  
2        primary endpoint. We'll be discussing this a  
3        little bit later in the presentation.

4                How about the results for FAST-2? In  
5        FAST-2, icatibant was effective in the treatment of  
6        acute HAE with the primary endpoint showing  
7        consistent onset of primary symptom relief in two  
8        hours compared to the median time of onset of  
9        10.1 hours with tranexamic acid, which was  
10       statistically significant.

11                To show you consistency of response, let's  
12        look at a few other measures. To allow a relevant  
13        comparison to FAST-3, we conducted that post hoc  
14        calculation of VAS-3 endpoint that was used in  
15        FAST-3. This calculation was taken from the  
16        prespecified and prospectively collected single VAS  
17        scores for FAST-1 and FAST-2. That should limit a  
18        potential for data bias, and we simply added the  
19        three prospectively collected single VAS scores and  
20        divided by three.

21                Given the typical HAE attack progression  
22        discussed by Dr. Lumry, the VAS-3 should reflect

1 the most problematic symptoms that the patient  
2 faces. As you see, icatibant demonstrates a  
3 consistent VAS-3 symptom relief in a median time of  
4 2.3 hours which was consistently separated from  
5 placebo and was statistically significant.

6 Now turning to FAST-2, conducting the  
7 post hoc calculations for the VAS-3 scoring, we  
8 again see that consistent icatibant response with a  
9 median time to onset of symptom relief, 2 hours.  
10 This also shows statistical superiority versus the  
11 comparator, tranexamic acid.

12 In looking at other secondary endpoints, as  
13 shown in FAST-1, icatibant was effective in the  
14 treatment of acute HAE with a secondary endpoint of  
15 time to almost complete symptom relief in  
16 10.5 hours. This was compared to the median time  
17 of almost complete symptom relief of 19.4 hours  
18 with placebo. Please note that we've again  
19 extended the X axis out to 120 hours to represent  
20 this longer term evaluation for symptom resolution.  
21 While there was consistent separation, the results  
22 were not statistically significant.

1           As shown here, icatibant in FAST-2 was  
2 effective in the treatment of acute HAE with a  
3 secondary endpoint of time to almost complete  
4 symptom relief in 10 hours compared to the median  
5 time of almost complete symptom relief of  
6 42.5 hours with tranexamic acid, and that was  
7 statistically significant.

8           Now, FAST-1 did not meet its primary  
9 endpoint as discussed in the briefing book, so  
10 let's review the data from that study. This is an  
11 important discussion point since we regard the  
12 results from FAST-1 as supportive and the icatibant  
13 results consistent to what we've seen in FAST-2 and  
14 FAST-3. However, the placebo group did perform  
15 much better than expected based on historical data.

16           A number of issues were noted when we looked  
17 at the data which may have contributed to  
18 differences in response to the placebo group, and  
19 this was discussed also in your briefing book.  
20 Recall that FAST-1's primary endpoint was time to  
21 onset of primary symptom relief, which relied on  
22 that single primary VAS. Since symptoms may evolve

1 during the attack, the single primary VAS may not  
2 quite represent the constellation of symptoms that  
3 patients may have.

4 FAST-1 had a greater number of patients with  
5 abdominal attacks. Those patients typically have a  
6 time of onset of symptom length that was shorter  
7 than patients with cutaneous attacks. And there  
8 were also a greater percentage of patients with  
9 severe symptoms at baseline of FAST-1. Severe  
10 patients also typically have a shorter time to  
11 onset of symptom relief compared to other patients.

12 Also, it's interesting that the placebo  
13 patients in FAST-1 had a longer time from attack  
14 onset to actual dosing, which means they were later  
15 in the progression of their HAE attack, and also  
16 patients in FAST-1 used pain meds early and more  
17 often after a placebo dosing. This may temporarily  
18 blunt a single symptom score such as pain, but it  
19 may not affect the course of other symptoms. So as  
20 I mentioned previously, the time to onset of  
21 symptom relief by composite VAS, that spectrum of  
22 symptoms, was significantly better for icatibant

1 than placebo in FAST-1 in contrast to the results  
2 using a single primary VAS.

3 Although the placebo group had some  
4 differences in response where those factors may  
5 have contributed, the icatibant results were  
6 constant across the three phase 3 studies with  
7 icatibant showing a median time to onset of  
8 response of 2 hours.

9 Now, let's look at the efficacy of icatibant  
10 in the repeat treatment of HAE attacks. We  
11 evaluated icatibant efficacy in subsequent attacks  
12 by following the patients in the open label  
13 extensions of the three FAST trials. For the data  
14 cutoff, we evaluated data from patients with at  
15 least five attacks with icatibant.

16 When you look at the median time to onset of  
17 symptom relief, based on that VAS-3, for icatibant,  
18 the Kaplan-Meier curves overlay each other with  
19 medians ranging from 1.5 to 2.4 hours across the  
20 first five icatibant-treated attacks, demonstrating  
21 there was no reduction in efficacy across repeat  
22 treatment of multiple HAE attacks.

1           These results were similar to what was seen  
2 with icatibant in the controlled portion of the  
3 study, and across the first five icatibant-treated  
4 attacks, in 94 percent of cases, a single injection  
5 of icatibant was used. This result was consistent  
6 with the limited use of rescue medication by  
7 icatibant-treated patients in the controlled phase.

8           Importantly, we also have data from  
9 38 patients treated for more than five attacks,  
10 with one patient treated for 142 attacks over a  
11 three-year time period. This gives us confidence  
12 that icatibant will continue to benefit patients  
13 with repeat use.

14           Let's look at efficacy in laryngeal attacks.  
15 HAE attacks that result in laryngeal edema are  
16 rare, but they're among the most serious type of  
17 attacks. In FAST-3, we did attempt to randomize  
18 patients to mild or moderate laryngeal symptoms to  
19 either icatibant or placebo; however, all patients  
20 did end up receiving icatibant.

21           To demonstrate icatibant efficacy for the  
22 treatment of laryngeal attacks, we analyzed 21

1 laryngeal attacks across the controlled and open  
2 label extension phases of FAST-3. The results for  
3 the laryngeal attacks treated with icatibant were  
4 similar to the results for the non-laryngeal  
5 attacks treated with icatibant with the median time  
6 to onset of symptom relief by the VAS-5 of  
7 2.2 hours and the median time to onset of primary  
8 symptom relief, 2.2 hours. And the laryngeal  
9 attacks treated with icatibant resolved with a  
10 median time of 6.2 hours as measured by the almost  
11 complete symptom relief.

12 To get more data on laryngeal attacks, we  
13 looked across all three FAST studies, and we see a  
14 similar response when looking at the laryngeal  
15 endpoint common to all three of these studies, the  
16 time to initial symptom improvement for the  
17 laryngeal attacks. Among the 60 patients with  
18 laryngeal attacks, icatibant produced a patient-  
19 assessed median time to onset of initial symptom  
20 improvement of .6 hours, which is similar to that  
21 seen for the cutaneous and abdominal attacks used  
22 in the same outcome measure. The response in

1 laryngeal attacks is comparable to the response  
2 we've seen in the non-laryngeal attacks.

3 To show consistency of the icatibant  
4 efficacy, let's look at subgroups. Regardless of  
5 the demographic or the subgroup, icatibant produced  
6 a consistent response as shown by the hazard ratio  
7 graphic where a ratio greater than 1 demonstrates a  
8 benefit over the control group. When examined by  
9 age, gender, weight, attack site, or attack  
10 severity, we see a consistent response with the  
11 average hazard ratio of 2.42 and all error bars  
12 above 1, demonstrating a clear advantage over the  
13 comparator group.

14 Overall, the three trials of icatibant  
15 showed significant response compared to either  
16 placebo in FAST-1 and FAST-3 or tranexamic acid in  
17 FAST-2 as shown by the hazard ratios for the  
18 endpoint time to the onset of symptom relief.  
19 Icatibant consistently had an onset of action and a  
20 median of approximately 2 hours for an onset of  
21 symptom relief.

22 In summary, our data show that icatibant

1 produces rapid and clinically meaningful results  
2 that demonstrate a quick symptom relief and  
3 resolution following an acute HAE attack versus the  
4 comparator. Efficacy has been shown regardless of  
5 an anatomical attack location, including cutaneous  
6 abdominal and laryngeal attacks. Across the  
7 prospective primary and secondary endpoints as well  
8 as the post hoc assessments, icatibant demonstrated  
9 a remarkably consistent efficacy across the  
10 controlled phase of the three phase 3 studies with  
11 a clinically meaningful magnitude of effect. These  
12 data also confirm the reproducibility of HAE  
13 efficacy from repeat treatment of subsequent  
14 attacks.

15 Overall, the clinical data show that a  
16 single 30-milligram icatibant sub-Q injection can  
17 manage most HAE attacks, and should the patient  
18 need additional treatment, they can take up to a  
19 total of three injections.

20 Let's examine the safety of icatibant. Our  
21 safety comes from the three phase 3 trials. To  
22 best represent icatibant safety, I'll be focusing

1 on the pooled data from FAST-1, FAST-2 and FAST-3.  
2 As presented in your briefing book, I'll also be  
3 discussing two populations, safety or the control  
4 population, which encompasses that first dose for  
5 patients in the control phase of the FAST studies.  
6 And I'll be discussing then the safety of icatibant  
7 in the open label or repeat treatment extension,  
8 which we call the treated or the repeat treatment  
9 population. And finally, I'll present safety data  
10 from the open label trial, the EASSI trial, that  
11 evaluated safety when icatibant was self-  
12 administered by patients.

13 So let's first look at the total number of  
14 exposures to icatibant. This slide summarizes  
15 exposure as of the cutoff at the time of  
16 submission. During the controlled and open label  
17 extension phases of the controlled phase 3 studies,  
18 225 patients received icatibant. Overall, 987  
19 attacks were treated with icatibant in the FAST-1,  
20 FAST-2 and FAST-3 studies. The mean number of  
21 icatibant-treated HAE attacks per patient was 3.7,  
22 and this ranged up to 142 attacks. Patients have

1 remained on study up to 36 months.

2           In the phase 3 safety population, which  
3 included all randomized patients from the three  
4 controlled phase 3 studies and their first attack,  
5 the mean age was similar to icatibant and the  
6 placebo groups. Approximately two-thirds of  
7 patients in the treatment groups were female, and  
8 the majority of patients in all treatment groups  
9 were white. The mean weights were similar across  
10 treatment groups.

11           Let's look at the primary adverse event that  
12 is seen in most patients. Since the early  
13 development of icatibant, it's been clear that  
14 localized injection site reactions following sub-Q  
15 administration of icatibant is common, but these  
16 reactions are transient and self-resolving. The  
17 most common reaction was erythema, seen in  
18 96 percent of patients. Since most icatibant-  
19 treated patients had transient erythema and  
20 swelling, information on these events was collected  
21 via prompted questioning of the patients and  
22 reported separately from other AEs.

1           Here you see the time of the initial  
2 injection. Within 30 minutes, the majority of  
3 patients report redness or erythema that's evident  
4 around the injection site, and this picture  
5 represents a moderate case which was reported in  
6 about half the patients treated with icanitabant.  
7 Within two hours, the erythema has subsided, and  
8 then it ultimately resolves.

9           As a reminder, adverse events are graded by  
10 physicians as mild, moderate to severe, but this is  
11 separate from what we call serious adverse events,  
12 meaning, for example, that you require  
13 hospitalization or some major intervention. You  
14 could have a severe event like erythema, but it's  
15 not considered a serious adverse event. When  
16 looking at what the patients and physician called  
17 severe injection site reactions, we find that  
18 24.8 percent had severe reactions of erythema. For  
19 the other symptoms, the majority of patients had  
20 only mild to moderate symptoms. None of these  
21 injection site reactions led to study  
22 discontinuation or required treatment. There are

1 no serious adverse events related to injection site  
2 reactions.

3 So I'd like to now review the non-injection  
4 site adverse events. Adverse events were collected  
5 throughout the observation period from the time of  
6 dosing through day 14. The overall incidence of  
7 adverse events was similar to placebo in evaluating  
8 events when you exclude those injection site  
9 reactions.

10 Adverse events were experienced by  
11 approximately 42.5 percent of patients in the  
12 icatibant group and by 54.7 percent of patients in  
13 the placebo group. There were seven severe adverse  
14 events for icatibant, 6.2 percent, and 14 for  
15 placebo, 18.7 percent. There were no deaths,  
16 hospitalization, or study discontinuations on  
17 icatibant.

18 Looking more in depth, here are the events  
19 that occurred in more than 2 percent of the  
20 patients in any group regardless of causality.  
21 Please note that all adverse events were reported  
22 in the briefing book. The adverse event most

1 frequently by patients was worsening or recurrence  
2 of HAE. Given the nature of an HAE attack, the  
3 severity of symptoms of an HAE attack can worsen  
4 after presentation to the physician or wax and wane  
5 during the attack, depending on medications that  
6 are used. These events are considered disease  
7 related, and this type of event is expected to  
8 occur in all treatment groups. This data was  
9 collected to better understand the disease course,  
10 and the events were generally mild to moderate and  
11 easily managed by patients.

12 Turning to severe adverse events, as I  
13 mentioned, there were seven severe AEs during the  
14 14-day period after the single dose, and they're  
15 outlined here. 4.4 percent of icatibant patients  
16 had a new attack, which was called severe, and  
17 14.7 percent of placebo patients had a new attack.  
18 None of the icatibant events became serious.

19 During the 14-day observation period of the  
20 control trial, only one SAE was reported for  
21 icatibant, a case of cystitis. There was one  
22 patient on tranexamic acid who became pregnant and

1 three placebo patients with serious events,  
2 including an MI, worsening HAE, and  
3 gastroenteritis. None of these SAEs were  
4 considered to be treatment related by the  
5 investigator.

6 Now, let's look at the repeat treatment  
7 population. The phase -3-treated population  
8 includes both the controlled and open label phases  
9 of the phase 3 studies, including the first attack  
10 and then treatment for later attacks. And this  
11 allowed us to examine the safety of icatibant over  
12 multiple attacks.

13 To show the consistency of icatibant safety,  
14 we've examined the adverse event data from the  
15 first five attacks. As you see, the reports of  
16 adverse events, severe adverse events, and serious  
17 adverse events are similar across each attack. The  
18 specific events are provided in your briefing book.  
19 There are no deaths or discontinuations due to AEs.  
20 This safety profile was maintained in the data that  
21 we have for patients who are treated beyond five  
22 attacks.

1           Since anaphylaxis and antibody formation is  
2 an area of concern for existing HAE therapies, we  
3 examined the immunogenicity potential for  
4 icatibant. After repeated treatment for multiple  
5 attacks over time in the phase 3 studies, there was  
6 no evidence of immunogenicity for up to 82 attacks  
7 over two years. Only three patients ever tested  
8 positive for anti-icatibant antibodies. One  
9 patient in FAST-1 tested positive at pretreatment  
10 and after initial icatibant treatment, indicating a  
11 patient's specific high background signal level.

12           Two patients in FAST-2 testified positive  
13 for anti-icatibant antibodies after repeat  
14 icatibant treatment. However, the positive results  
15 were transient. These patients continued treatment  
16 ultimately with no further antibodies and no effect  
17 on safety and efficacy. All three patients who  
18 tested positive for anti-icatibant antibodies,  
19 maintained efficacy over the treatment period, and  
20 no patients in FAST-3 tested positive for anti-  
21 icatibant antibodies after repeat treatment up to  
22 five attacks. Consistent with this lack of

1 immunogenicity, no hypersensitivity or anaphylactic  
2 reactions were reported in any patient treated with  
3 icatibant.

4           The FAST-3 phase 3 study shows that  
5 icatibant is effective and well tolerated. As  
6 Dr. Lumry discussed, patients want self-  
7 administration for their HAE attacks to help ensure  
8 ready access to therapy. Since in our own survey  
9 of hospitals, we found that, at most, 50 percent of  
10 hospitals don't even carry therapies to treat acute  
11 attacks of HAE, so we also wanted to understand the  
12 safety of icatibant when self-administered by the  
13 patient in a trial called the EASSI study.

14           This study is discussed in the briefing  
15 book, and enrolled patients could be naïve to  
16 icatibant or they may have received icatibant in a  
17 previous trial. The first HAE attack for icatibant  
18 naïve subjects enrolled in the study was treated at  
19 the study site where a physician could administer  
20 icatibant to the patient. After receiving their  
21 first treatment with icatibant, these patients were  
22 then eligible for self-admin.

1 All patients were trained on the method of  
2 self-administration at the enrollment visit. The  
3 training materials also provided information on how  
4 to self-diagnose an HAE attack and how to decide  
5 when to treat. Patients were given a syringe  
6 containing icatibant to use in the event of an HAE  
7 attack and decided based on his or her perceived  
8 need for acute treatment whether they should treat  
9 or not.

10 The patient self-administered one  
11 30-milligram sub-Q injection of icatibant at home  
12 or at some other place convenient to them but not  
13 at the investigational site nor under the  
14 supervision of a physician. As necessary, patients  
15 could return to the study site for up to two  
16 additional injections of icatibant, and these  
17 injections were administered by a healthcare  
18 provider.

19 When we look at self-administration, we also  
20 see a consistent safety profile for icatibant that  
21 is similar to the phase 3 studies. Importantly, no  
22 new safety issues were identified. Thirty-two

1 percent of the patients that self-administered  
2 reported adverse events, excluding those injection  
3 site reactions. Fourteen of the 18 adverse events,  
4 or 78 percent, were considered mild to moderate by  
5 the patients. There were no serious adverse events  
6 or treatment discontinuations and no  
7 hypersensitivity observed.

8 Evaluation of the HAE patient history shows  
9 that patients are very familiar with the symptoms  
10 and presentation of HAE attacks, leading to  
11 clinical recommendation for self-administration.  
12 To examine patient interest and awareness, Shire  
13 conducted a survey of patients who self-injected  
14 during the EASSI trial. Subjects were able to  
15 self-diagnose and self-treat without difficulty,  
16 and only two of 56 subjects required a second  
17 injection of icatibant for treatment of a single  
18 attack.

19 In response to this survey, all 56 subjects  
20 said that the training materials were sufficient or  
21 very sufficient to explain the method of self-  
22 administration. When asked if it was difficult to

1     prepare the injection site before the injection,  
2     all subjects said it was easy or very easy.  Nearly  
3     all responded that it was easy or very easy to  
4     assemble and handle a syringe.  Only two of the 56  
5     patients found it difficult or very difficult to  
6     inject.  And 95 percent of the patients said that  
7     self-administration was preferable or very  
8     preferable to administration in the clinic.

9             In summary, sub-Q icatibant 30 milligrams  
10     consistently demonstrated an acceptable safety  
11     profile as shown from the integrated analyses of  
12     the pooled data from the three controlled phase 3  
13     studies.  Self-limited, localized injection site  
14     reactions occurred in most patients treated with  
15     sub-Q icatibant; however, these were mild to  
16     moderate in severity and resolved quickly after  
17     icatibant administration without any need for  
18     intervention.

19             The overall occurrence of other adverse  
20     events was relatively low with most regarded as  
21     mild to moderate in nature.  Importantly, no  
22     adverse events led to discontinuation or

1 hospitalization. In addition, the safety profile  
2 of self-administered icatibant was consistent with  
3 that seen in the controlled studies.

4 Icatibant appears to be minimally  
5 immunogenic, and we've seen no reports of  
6 hypersensitivity or anaphylactic reactions with  
7 icatibant. The safety profile seen across repeat  
8 treatments with icatibant was consistent with that  
9 seen for the icatibant group in the controlled  
10 phase of the phase 3 studies. All this supports  
11 the overall safety profile for icatibant.

12 Thank you. I'd now like to invite Dr. Marc  
13 Riedl to give you an overview of the clinical  
14 relevance of the data and the ability of patients  
15 to safely use icatibant.

16 **Sponsor Presentation - Marc Riedl**

17 DR. RIEDL: Thank you, Dr. Cammarata.

18 I'd also like to thank the Chair and members  
19 of the advisory committee for the opportunity to  
20 share my clinical perspective about the results of  
21 the icatibant trials and the likelihood that  
22 approval of this novel treatment will fulfill the

1 unmet medical needs delineated earlier by  
2 Dr. Lumry.

3 I've been treating HAE patients for the past  
4 10 years and clinically manage over 60 HAE  
5 patients. I've also worked closely with the U.S.  
6 Hereditary Angioedema Association, the leading  
7 patient support organization for HAE, which we'll  
8 hear from later today. As a matter of disclosure,  
9 I have been a scientific advisor, an investigator,  
10 and a consultant for Shire. I'm speaking as both  
11 an investigator and a clinician because I believe  
12 that icatibant is an important new treatment for  
13 patients with HAE and will significantly impact the  
14 management of this condition.

15 As discussed by Dr. Lumry, on-demand  
16 administration of HAE therapy can facilitate early  
17 intervention. The literature suggests that  
18 immediate access and self-administration of acute  
19 therapies reduces attack severity and duration,  
20 improves HAE-related quality of life, and decreases  
21 time lost from work, school and leisure activities.

22 Self-administration is currently endorsed by

1 all published HAE guidelines, including those from  
2 the U.K., Denmark, and Canada as well as an  
3 international guideline document. These guidelines  
4 recommend that after a diagnosis is confirmed,  
5 every HAE patient should be considered for self-  
6 administration of acute therapy, also known as  
7 on-demand therapy. The benefits and risks for each  
8 patient should be considered before a decision is  
9 made. My presentation will focus on how icatibant  
10 would fit into my current HAE treatment paradigm.

11 Treatment of HAE in the U.S. has  
12 historically focused on chronic prophylaxis to  
13 prevent attacks in appropriate patients and more  
14 recently has included on-demand treatment as newly  
15 approved effective medications have become  
16 available. The goal of prophylaxis is to reduce  
17 HAE attack frequency and severity, and the  
18 literature suggests that approximately 40 to  
19 50 percent of U.S. HAE patients receive long-term  
20 prophylactic therapy.

21 In my practice, the patients that I consider  
22 for prophylactic therapy include those that have

1 frequent HAE attacks, often more than one attack  
2 per month; patients that have frequent debilitating  
3 attacks -- and in particular, abdominal or  
4 laryngeal symptoms -- that cause significant  
5 interference with their daily activities, including  
6 work or school; and, also, patients that are unable  
7 to maintain an acceptable quality of life using  
8 only on-demand acute therapies.

9           The available prophylactic treatments  
10 include attenuated androgens, anti-fibrinolytics,  
11 and fresh frozen plasma, which are used exclusively  
12 for short-term pre-procedural prophylaxis. In  
13 October of 2008, a nano-filtered human plasma-  
14 derived C1 inhibitor concentrate, or Cinryze, was  
15 approved for long-term HAE prophylaxis. However,  
16 there are limitations with the primary medications  
17 currently used for HAE prophylaxis in the United  
18 States, mainly the androgens and nano-filtered  
19 plasma-derived C1 inhibitor.

20           Long-term prophylaxis is very useful, but  
21 patients and physicians are frequently concerned  
22 with the long-term side effects and the potential

1 impact of chronic treatment. With androgen  
2 therapy, the side effects include hepatotoxicity,  
3 hypocholesterolemia, and virilization in women.  
4 Long-term twice weekly treatment with IV plasma C1  
5 inhibitor can lead to vascular complications.

6 In addition, while prophylaxis can reduce  
7 the frequency and the severity of HAE attacks,  
8 acute swelling episodes still occur for many of  
9 these patients, necessitating availability of acute  
10 treatments. As a result, both physicians and  
11 patients wish to optimize on-demand therapy, which  
12 will benefit all HAE patients regardless of their  
13 disease severity. The advent of more acute care  
14 therapies will further encourage this evolution.

15 So what are our current on-demand choices  
16 for HAE attacks? The treatments used for acute  
17 attacks have historically included fresh frozen  
18 plasma which is given intravenously. This has  
19 several risks associated with its use, including  
20 infusion reactions, exacerbation of attack symptoms  
21 in rare instances, and the potential transmission  
22 of viral disease.

1           A human plasma-derived C1 inhibitor, or  
2     Berinert, was approved by the FDA in December of  
3     2009 for the treatment of facial and abdominal  
4     attacks in adolescents and adults. This is given  
5     as an intravenous infusion and generally infused by  
6     a healthcare provider. The risks associated with  
7     C1 inhibitor use include vascular complications,  
8     and as with any plasma product, the possible  
9     transmission of viral or prion-associated diseases.

10           Kalbitor, a selective plasma kallikrein  
11     inhibitor, was approved in November of 2009 for the  
12     treatment of all types of HAE attacks in  
13     individuals 16 years old and older. The product is  
14     administered subcutaneously and is given by a  
15     healthcare professional in a setting where  
16     anaphylaxis can be recognized and treated since  
17     confirmed hypersensitivity reactions have been  
18     associated with the use of this medication. So  
19     there remains a need for products that can provide  
20     rapid, on-demand, self-administration outside of  
21     the hospital or clinic.

22           Now, due to the spontaneous and

1 unpredictable nature of HAE attacks, every one of  
2 my patients with HAE needs rapid access to an  
3 effective on-demand acute therapy. And while there  
4 are effective acute care treatments for HAE, there  
5 are some additional challenges beyond the safety  
6 profiles that create barriers to rapid treatment  
7 access.

8           The current treatments typically require  
9 trips to the clinic or hospital for administration  
10 by a healthcare professional. This leads to delays  
11 due to transportation to the site, registration,  
12 diagnosis and administration of the medication, as  
13 Dr. Lumry discussed earlier. The available  
14 C1 inhibitor products require some technical  
15 training, as in the IV preparation and  
16 administration of the therapy.

17           Yet, even with the ability to overcome these  
18 issues with a product like icatibant, can HAE  
19 patients adequately self-diagnosis and self-treat?  
20 In my experience, they can. Patients have this  
21 experience to recognize their HAE attack symptoms,  
22 stemming from their long history of repeated

1 attacks. My patients can recognize the onset of an  
2 attack early in the course, which makes early  
3 treatment possible if medication is readily  
4 accessible.

5 At present, these early symptoms lead  
6 patients to our office or to the emergency  
7 department for treatment with the result in travel  
8 and treatment delays that we've discussed. The  
9 patient experience and the ability to readily  
10 recognize attack onset are the reason why HAE  
11 guidelines recommend self-administration. I and  
12 other HAE experts agree that patients can  
13 accurately self-diagnose attacks. There's a  
14 direct benefit from self-diagnosis of an HAE  
15 attack, if we can accelerate the time from seeking  
16 care to the administration of therapy.

17 Of equal importance, studies demonstrate  
18 that HAE patients can be taught to correctly and  
19 safely self-administer on-demand therapy. This is  
20 confirmed by experience from Europe, and Dr. Marcus  
21 Maurer is here today to offer his experience with  
22 about 50 German self-administration patients using

1         icatibant, many of whom have submitted letters to  
2         this committee in support of icatibant self-  
3         administration.

4                From the clinical standpoint, I want to  
5         address what's needed by physicians and patients in  
6         treating HAE attacks and how that ties to the data  
7         that you've seen today.  First, we need an agent  
8         that provides reliable and early intervention for  
9         all types of HAE attacks.  The reality with my HAE  
10        patients is that early intervention reduces the  
11        need for hospitalization and the duration of  
12        attacks.  And early treatment is essential to  
13        prevent disability and complications that occur  
14        with progressive attacks.  The ability to treat  
15        attacks early allows patients to feel self-  
16        sufficient and in control of their lives and  
17        independent from the emergency room or their  
18        doctor's office.

19               We have a need to reduce the barriers to  
20         treatment access and to accelerate the initiation  
21         of therapy as can be done with  self-  
22         administration.  Right now, the arrangements for

1 acute HAE treatment are complicated by the need to  
2 go to a clinical site for care. For attacks that  
3 may occur at any time, on any day, this often ties  
4 patients to their home location since travel leads  
5 to unreliable treatment access. And even with a  
6 knowledgeable physician nearby, each patient  
7 requires individualized arrangements with their  
8 local hospital to ensure that on-demand treatment  
9 is available for immediate access when necessary.

10 These access barriers are not adequately  
11 reflected in HAE clinical trials where a research  
12 physician is awaiting a patient's arrival. In  
13 reality, a patient with an HAE attack needs to wade  
14 through the necessary paperwork, the waiting rooms,  
15 and the triage procedures before they can receive  
16 their care.

17 Providing HAE patients with a self-  
18 administration option significantly reduces these  
19 barriers and gives the patient the ability to start  
20 treatment without travel, without concern about  
21 medication availability, and without these  
22 unnecessary delays. Earlier intervention can help

1       lessen attack severity and recovery time.

2               We've seen today the clinical study data for  
3       icatibant. These data provide confidence that  
4       icatibant provides consistent efficacy for HAE  
5       attacks at all anatomical locations and that this  
6       efficacy is reliable over repeated attacks.

7       Secondly, icatibant appears to have a very good  
8       safety profile and is well tolerated by patients.  
9       These results align with my own personal experience  
10      with icatibant as an investigator in the FAST-1 and  
11      FAST-3 trials.

12              This efficacy and safety profile is the key  
13      feature for an acute treatment that can be used  
14      outside of a healthcare center to allow for early  
15      intervention at the time of an HAE attack. With  
16      the subcutaneous route of administration, I'm  
17      confident that most patients are capable of  
18      learning to properly administer this product. But  
19      this is not a one-size-fits-all situation, and the  
20      management of HAE still requires an individualized  
21      approach.

22              In order to self-administer icatibant,

1 physicians and patients will need to discuss a  
2 number of topics. These include the benefits and  
3 risks for all the available treatment options for  
4 acute attacks; ensuring that patients can recognize  
5 when to use icatibant, and based on consensus  
6 guidelines treatment should occur at the earliest  
7 signs and symptoms of angioedema; recognizing the  
8 potential side effects of icatibant, including the  
9 common injection site reactions; a plan of action  
10 should be established in the event of attack  
11 progression, including the need to seek care for  
12 any laryngeal attack following self-administration.

13 Patients will need a clear understanding of  
14 the proper storage, preparation and administration  
15 of icatibant and also an acceptable plan for  
16 recordkeeping and reporting of attacks and  
17 injections. This should be arranged. Finally,  
18 periodic follow-up with a physician is necessary  
19 for the clinical management and the review of their  
20 treatment plan.

21 So, in summary, HAE is a life-altering and  
22 life-threatening chronic condition which adversely

1 affects the physical, psychological and social  
2 health of HAE patients. While prophylactic and  
3 acute treatments are available, these do not  
4 completely fulfill the medical needs of many  
5 patients. In treating HAE, we need a medication  
6 that will facilitate early intervention for most  
7 patients and allow self-administration for when  
8 their attacks occur. This will allow patients  
9 increased independence and quality of life.

10 Icatibant has been shown in clinical studies  
11 to be effective and safe and provides the  
12 opportunity for self-administration with early  
13 intervention. This will fulfill an important unmet  
14 need for HAE patients.

15 Dr. Cammarata will now summarize the  
16 presentation.

17 **Sponsor Presentation - Sue Cammarata**

18 DR. CAMMARATA: Thank you, Dr. Riedl.

19 I'd now like to summarize the data that  
20 supports the icatibant risk benefit. The benefits  
21 of icatibant are demonstrated in FAST-3 and are  
22 supported by FAST-1 and FAST-2. The efficacy is

1 best represented by rapid time to symptom relief,  
2 and this is a conservative measure requiring three  
3 consecutive measurements of at least a 50 percent  
4 improvement in symptoms. And it's also supported  
5 by attack resolution as measured by the time to  
6 almost complete symptom resolution.

7 The studies show a consistent efficacy  
8 response across symptoms and over multiple attacks,  
9 and importantly, these two measures also align with  
10 the important efficacy needs identified by  
11 patients. The phase 3 studies also demonstrate a  
12 consistent safety profile for icatibant  
13 30-milligram sub-Q injections. The main adverse  
14 event, erythema and swelling at the injection site,  
15 was observed in almost all patients in the trials.  
16 However, these are generally mild to moderate and  
17 transient. Importantly, there were no instances of  
18 hypersensitivity or deaths on icatibant.

19 The benefit-risk profile shown in the  
20 clinical program supports the opportunity for self-  
21 administration, which is an important goal for HAE  
22 patients. Yet, even with this benefit-risk

1 profile, we recognize that the safety database for  
2 this rare condition merits activities to support  
3 appropriate patient self-administration. Thus,  
4 Shire has proposed post-approval activities to help  
5 protect patient safety.

6 As Drs. Lumry and Riedl have presented, HAE  
7 patients are educated and do actively participate  
8 in their HAE treatment. They can distinguish  
9 attack onset and attack resolution from other  
10 symptoms, allowing them to know when to seek  
11 treatments and when to seek interventions. Thus,  
12 we'll seek to provide information on the  
13 appropriate use of icatibant that fits into their  
14 knowledge base.

15 The icatibant packaging will include a  
16 proposed patient leaflet that describes the correct  
17 use of icatibant along with information on use of  
18 the self-injector syringe. This will support  
19 information and instructions found in the labeling  
20 and provided to physicians to facilitate patient  
21 discussions, including when to seek help. For  
22 example, we recommend that all patients who

1 experience laryngeal attacks seek professional care  
2 immediately after self-administration.

3 Additionally, Shire will use existing patient  
4 support systems like a toll-free patient support  
5 center and website to aid patient education.

6 Shire HGT is currently investigating options  
7 to partner with a healthcare service provider that  
8 patients and physicians can choose to use on  
9 training on HAE and icatibant use. Next, Shire HGT  
10 is currently developing a training kit to be used  
11 during injection training, including an artificial  
12 abdomen for practice. And Shire will also be using  
13 targeted surveillance whereby reports of pre-  
14 identified adverse events of special interest could  
15 trigger more of active acute investigations. And  
16 this would include things like hypersensitivity and  
17 cardiac events. We believe that these measures  
18 will appropriately support safe use of icatibant,  
19 including self-administration and support the  
20 product approval.

21 When considering the rarity of this orphan  
22 condition and in comparisons to other HAE

1 submissions, we have a large database. The core of  
2 the icatibant clinical development program  
3 encompasses three controlled phase 3 studies and  
4 their open label extensions as well as the open  
5 label phase 3 self-administration trial. This  
6 includes 236 patients to whom icatibant was  
7 administered by a healthcare provider and 56 who  
8 self-administered icatibant for the treatment of  
9 acute HAE attacks. At the time of submission,  
10 there were a total of 1,055 acute attacks of HAE  
11 treated with sub-Q icatibant in clinical trials,  
12 including 60 patients who had laryngeal attacks.

13 We also have a relatively large HAE clinical  
14 dataset for repeat attacks, and that also includes  
15 38 patients who were treated with icatibant beyond  
16 five attacks. In addition to exposure in clinical  
17 studies, it's estimated that there have been 8,000  
18 patient exposures from the time of European  
19 approval through January of this year.

20 We feel that the totality of this data  
21 demonstrate the efficacy and safety profile for  
22 icatibant. Thank you.

1 Dr. Krishnan, I'd be happy to answer  
2 questions.

3 **Clarifying Questions for Sponsor**

4 DR. KRISHNAN: Great. Thank you very much,  
5 Dr. Cammarata.

6 We will now ask if the committee has  
7 questions for the sponsor.

8 Yes?

9 DR. BORISH: Two quick questions and a slow  
10 one.

11 Can someone tell me what a -- in terms of  
12 the potential for immunogenicity, could someone  
13 tell me what a non-proteinogenic amino acid is?

14 DR. CAMMARATA: Yes. Actually, I would have  
15 Dr. McCauley or Peri, and then we also have a slide  
16 of the structure.

17 DR. BORISH: That would be great if you'd  
18 put the slide up.

19 DR. CALIAS: My name is Peri Calias. I'm  
20 senior director of non-clinic development for Shire  
21 HGT. And icatibant is a decapeptide. It is a  
22 synthetic peptide with a structure similar to

1 bradykinin. There are five non-proteinogenic amino  
2 acids, one D and four mimetics. It's very highly  
3 selective for the B2 receptor.

4 DR. KRISHNAN: Please use the microphone.  
5 Thank you.

6 DR. BORISH: I know what the word "D" was.  
7 What's a mimetic amino acid?

8 DR. CALIAS: A non-natural amino acid.

9 DR. BORISH: Okay. Thank you.

10 So it's certainly something foreign that the  
11 body would recognize as such.

12 DR. PLATTS-MILLS: Can we get better  
13 clarification of this? Can you show us the  
14 structure of bradykinin and the structure of  
15 icatibant?

16 DR. CALIAS: We do not have the structure of  
17 bradykinin as such, but we can get that for you on  
18 the break.

19 DR. BORISH: Second is a pharmacokinetic  
20 question, but I thought I read that the drug was  
21 largely clear after one hour. And maybe this will  
22 be more relevant later when we have a more

1 freebasing discussion. But the recommendations are  
2 that it could be repeated after six hours. And  
3 certainly there are a lot of people not having  
4 relief at one hour.

5 Why wait another five hours?

6 DR. CAMMARATA: I would ask Dr. McCauley to  
7 talk about the PK/PD around icatibant, please.

8 DR. MCCAULEY: Sure. Slide up, please.

9 In answer to the question, you're correct  
10 that the -- first of all, Tom McCauley, I'm  
11 director of clinical pharmacology and  
12 pharmacokinetics at Shire HGT. And in answer to  
13 your question, you're correct that the  
14 pharmacokinetic half-life is sort of multiphasic,  
15 but the bulk of the amplitude is dropped over a  
16 period of about one to two hours. So it does have  
17 a very short pharmacokinetic half-life.

18 But as you can see, with a 30-milligram  
19 dose, the plasma concentration is sort of met here,  
20 which is sort of a mean for some of the phase 1  
21 data filled with 97 patients here. The dotted  
22 yellow line represents the EC-50 for inhibition of

1 bradykinin-induced symptoms as derived from the  
2 bradykinin challenged model that Dr. Cammarata  
3 referred to. As you can see, the plasma  
4 concentration remains above the EC-50, well in  
5 excess of it for out to sort of six to eight hours.

6 DR. BORISH: Great. In some of the  
7 preclinical studies, there were some issues I think  
8 with fertility that were raised. And, again, in  
9 terms of the safety, the second question will  
10 answer the first. But what use is bradykinin, and  
11 is there a bradykinin receptor knockout mouse? And  
12 obviously, if there is, then the mice are plenty  
13 fertile. But is there a phenotype to knocking out  
14 the bradykinin 2 receptor?

15 DR. CAMMARATA: That's an interesting  
16 question.

17 DR. BORISH: In terms of fertility,  
18 infection, anything.

19 DR. CAMMARATA: Dr. Calias is going to  
20 comment.

21 DR. CALIAS: Peri Calias, senior director of  
22 nonclinical development for Shire HGT. All our

1 studies have been in wild-type mice, and in answer  
2 to the first part of the question you asked, what  
3 is bradykinin do?

4 DR. BORISH: Very simply, is there any  
5 useful purpose of that compound that there could be  
6 a problem in blocking it, especially in terms of  
7 fertility?

8 DR. CALIAS: Well, bradykinin is expressed  
9 upon a traumatic event. So it's important in wound  
10 healing, vasodilation, cardio protective effects.  
11 Fertility, I'm not aware of any protective effects  
12 in fertility with B2.

13 DR. BORISH: Because I think in your report,  
14 you talk about implantation specifically.

15 DR. CALIAS: Yes. So in our preclinical  
16 repro tox studies, icatibant was found, first off,  
17 to be nonteratogenic. But we did observe uterine  
18 distress and delayed parturition in the animals  
19 that received a very large cumulative dose compared  
20 to what an average HAE patient would receive. We  
21 are therefore recommending that patients of  
22 childbearing age discuss the risks and benefits

1 with their physician before taking icanitabant.

2 DR. KRISHNAN: Great. I'm just going to  
3 remind the committee members that if you have a  
4 question, please let Kristine know, and we'll then  
5 come to you in order. That way, we give an  
6 opportunity for other committee members to ask  
7 questions.

8 I think Mr. Mullins, you had a question to  
9 ask.

10 MR. MULLINS: Yes, I had two questions, one  
11 dealing with the protocol utilized to determine  
12 which patients were self-administered because it  
13 seems like we have a small population of patients  
14 within the 225 that self-administered. It looks  
15 like -- excuse me -- within the 236. It looks like  
16 less than 26 percent self-administered. So I want  
17 to understand what was the protocol used to  
18 determine who self-administered, who went on site  
19 to receive their injection.

20 Secondly, one of utmost concern, there seems  
21 to be eight cases that there were indications that  
22 women, pregnant women, seemed to have challenges,

1 either hypersensitivity to -- over 61 percent had  
2 problems, challenges with the therapy. And I know  
3 three went full term, two were aborted, and we  
4 don't know what happened to the other five. So I  
5 want to understand if Shire could expound on those  
6 results and that data. Thank you.

7 DR. CAMMARATA: I think I heard two  
8 questions. First was a little bit about the self-  
9 administration study, and the second was about  
10 pregnancies during the trials.

11 Is that correct?

12 MR. MULLINS: Yes, within the issue of  
13 pregnancy, pregnant women.

14 DR. CAMMARATA: Yes. The first, about the  
15 EASSI trial, which was a self-administration trial,  
16 that was a trial of 56 patients that could enroll  
17 into that study. Those patients could have been on  
18 icatibant in a previous trial, and 48 of those  
19 patients had been on icatibant in a previous trial.  
20 They also could have been naïve to treatment, where  
21 they never received icatibant previously. So for  
22 those patients, for their first attack, they came

1 in to see the doctor, they received their first  
2 injection from the physician, and then those  
3 patients were eligible then to get the self-  
4 administration portion.

5 So all 56 were involved in the self-  
6 administration portion, but they did receive -- all  
7 of them received instruction after a first  
8 injection from the physician at the clinic.

9 MR. MULLINS: One follow-up to that. What  
10 type of training did they receive on self-  
11 administration?

12 DR. CAMMARATA: They gave them training  
13 information that showed them how to use the  
14 injector kit and also information about HAE. As  
15 Drs. Lumry and Riedl stated, that the patients are  
16 very educated, they know their disease, and so they  
17 were able to use that information to self-inject.

18 MR. MULLINS: Wasn't at the time of that  
19 training -- was it a seminar or was it --

20 DR. CAMMARARA: It'd be in the office. It  
21 was one-on-one with the physicians at the time.

22 MR. MULLINS: What would you say the length

1 of time was spent on that training?

2 DR. CAMMARATA: Let's see.

3 Dr. Mauer, did you participate in the self-  
4 administration trial? You might want to comment on  
5 your training of patients in the self-  
6 administration study. Dr. Mauer is our -- from  
7 Germany where they do have self-administration  
8 approved.

9 DR. MAUER: I do. My name is Marcus Mauer.  
10 I'm a professor of dermatology and allergology at  
11 the department of dermatology Allergie-Charite,  
12 University Hospital, Berlin, Germany. I would also  
13 like to disclose that I was an investigator in the  
14 FAST trials, also in the EASSI trials, and I'm an  
15 advisor to Shire.

16 We run a large angioedema clinic with 108  
17 HAE patients. Most of them are on self-  
18 administration; about 60 of them are on icatibant.  
19 Now, those patients that were included in the EASSI  
20 trial received treatment if they were naïve to  
21 self-administration in the office. So we did it  
22 together with them when they came in, and we

1       trained them. We taught them how do it when they  
2       were with us.

3               We spent about 15 minutes on that, showing  
4       them how to handle the syringe, how to do the  
5       injection, how to take precautions. There's  
6       usually someone else from the family that is in  
7       that training session, and we repeat these training  
8       sessions both in the EASSI trials and when we teach  
9       patients outside of studies when patients request  
10      that.

11             We've done it for three years now, almost  
12      three years, and in the first two years that's  
13      outside of the EASSI trials, we've done it actually  
14      with placebo injections. So we had patients inject  
15      saline solution just the same way they would inject  
16      the icatibant while we were there teaching them how  
17      to do it. We now have that artificial abdomen for  
18      the last four weeks. We have that thing, and it's  
19      great because you can actually practice over and  
20      over again if you want on how to give the  
21      injection. So it's very helpful.

22             DR. CAMMARATA: In the information that we

1 have that we would provide, if patients could self-  
2 administer, that is part of the training package  
3 that's available to any patient who wishes to have  
4 that, including the access to the artificial  
5 abdomen.

6 The second part of your question was  
7 regarding pregnancies, correct? Okay. Yes,  
8 patients were not supposed to be pregnancy during  
9 the clinical trial, but there were some women that  
10 identified at some point during the trial. Some of  
11 these could have been quite a bit later than that  
12 trial, that there were some pregnancies in  
13 patients.

14 Dr. Bajwa, if you could just comment on the  
15 pregnancies and summarize those.

16 DR. BAJWA: Naghmana Bajwa, senior director,  
17 global pharmacovigilance and risk management. We  
18 had seven pregnancies reported, as Dr. Cammarata  
19 mentioned, any time during the trials. Four of  
20 those cases have had healthy outcomes, and we have  
21 followed up to receive information about that. One  
22 patient, we are awaiting on the outcome. The

1 pregnancy is ongoing. Another patient, the outcome  
2 has happened, and we are waiting on the outcome  
3 information. One case was elective termination,  
4 and that was for social reasons.

5 DR. CAMMARATA: And we are recommending -- I  
6 believe this is going to be a Class C label so that  
7 this is definitely a discussion between the patient  
8 and physicians. And we'll be discussing further  
9 with the FDA on appropriate labeling regarding  
10 that.

11 DR. KRISHNAN: Great. Thank you.

12 I will next recognize Dr. Foggs. I believe  
13 you have a question.

14 DR. FOGGS: Yes. I wanted to know what the  
15 basis was for the selection of 48 hours to define  
16 whether or not an episode of angioedema on the  
17 front side of 48 hours constituted an exacerbation  
18 versus an episode occurring on the backend of  
19 48 hours or after 48 hours, constituting a  
20 recurrence.

21 DR. CAMMARATA: You're correct that attacks  
22 can proceed and it varies in time from patient to

1 patient. In the case of the clinical trials here,  
2 the clinical trials were designed so that the first  
3 48 hours, yes, it was reported as a specific  
4 adverse event, and then it was collected as a new  
5 event after 48 hours. When we look at the course  
6 of an attack, much of the course of a normal  
7 attack, the peak is within those first 24 to  
8 48 hours, which is why it was recorded in that way.  
9 However, we did collect safety information looking  
10 at those events out to five days, also.

11 DR. KRISHNAN: Great.

12 Dr. Shepherd, a question?

13 DR. SHEPHERD: This is a question on  
14 immunogenicity. While I recognize that those  
15 patients who received repeat injections seemed to  
16 have both clinical efficacy and no signs of any  
17 side effects, I just wanted to clarify. My  
18 understanding is that you measured IgG specific for  
19 the drug in FAST-1 and 2, and in FAST-3, you  
20 measured IgG and IgE.

21 Can you first tell us what your positive  
22 controls were for those assays? And, secondly, can

1 you elaborate on those patients who received repeat  
2 injections? Were they analyzed and for how long?

3 DR. CAMMARATA: Dr. McCauley, you can  
4 comment.

5 DR. MCCAULEY: Tom McCauley, director of  
6 clinical pharmacology and PK from Shire.

7 I think there were sort of two parts to the  
8 question. I would refer the second. I'll answer  
9 the first part with regard to the positive controls  
10 and the assay, and I would refer to one of my  
11 colleagues for the longer-term immunogenicity  
12 screening data.

13 With regard to positive controls, in the  
14 FAST-1 and FAST-2 trials, it was a mirroring of  
15 positive control that was used; while in FAST-3, it  
16 was a hybrid chimeric human murine that was used  
17 for a positive control.

18 DR. CAMMARATA: And regarding the clinical  
19 data, we have the summary data for the three  
20 patients. So I can show you the data specifically  
21 for the three patients that we had those antibodies  
22 on, if you'd like.

1 DR. SHEPHERD: It's just to answer the  
2 question that beyond times zero, did you see any  
3 change? How many were analyzed at later dates?

4 DR. CAMMARATA: I'll go through each of the  
5 three patients.

6 Slide up. Now, this is the patient that  
7 was -- patient who had been followed and had  
8 different attacks. You see skin swelling,  
9 abdominal pain. This is different weeks from  
10 screening, their antibody status, the attack type,  
11 then they have the outcomes timed to onset of  
12 symptom relief, the primary, the time to almost  
13 complete symptom relief and then the time to  
14 initial symptom improvement.

15 So some of the signs you'll see these  
16 abbreviations. We found it was a lot easier to say  
17 TISI, TOSR and TACSR, but I will try to read them  
18 out for you. But for our slides, we've done it  
19 this way.

20 So you can see this is a patient who had  
21 skin swelling and abdominal pain in two different  
22 attacks. The efficacy was consistent.

1           Next slide. This patient is one which you  
2           can see who had numerous attacks and continued to  
3           use icatibant through repeat treatment. All of the  
4           patient's attacks were skin attacks. It was only  
5           on those early attacks where they had some positive  
6           antibodies. The rest were negative. Again, we're  
7           showing all of the outcome measures, and generally,  
8           the patient did well over time with those repeat  
9           injections. Same with safety.

10           Then the next patient, FAST-2. Next slide  
11           up. This shows the same thing. This is the third  
12           patient who had a couple episodes where they had a  
13           transient antibody positive. The rest were all  
14           negative. This patient had primary abdominal HAE  
15           attacks. Again, his or her outcome appeared to be  
16           consistently good despite those brief episodes of  
17           positive antibodies.

18           So overall, the efficacy of icatibant was  
19           maintained.

20           DR. KRISHNAN: Do you have a follow-up,  
21           Dr. Shepherd?

22           DR. SHEPHERD: A separate question just on

1 your methodology when patients develop symptoms and  
2 then went to the clinical site, you stated that  
3 you're entering patients with moderate symptoms  
4 into this study.

5           Could you elaborate? Did you wait, for  
6 example, until they developed moderate symptoms  
7 before treating? You obviously want them with a  
8 high VAS score to start with. Can you explain  
9 that?

10           DR. CAMMARATA: Yes. The patients and the  
11 physicians are aware that the requirement to enroll  
12 was the patient had to have moderate or severe  
13 symptoms as judged by the patient and the  
14 physician. And you're correct. The reason why is  
15 primarily you do want to make sure you have a score  
16 that's high enough that you can actually see a  
17 benefit. So that was a requirement that patients  
18 had to have moderate to severe symptoms in general.

19           DR. KRISHNAN: Great.

20           Dr. Greenberger, I think you're next.

21           DR. GREENBERGER: Thank you. My question  
22 focuses specifically on the time to initiation of

1 the treatment. It was different in the studies. I  
2 couldn't find it in the Ziccardi paper in the New  
3 England Journal in 2010.

4           Could you say if the trial was different or  
5 the treatment was different in like 10 hours versus  
6 six hours?

7           DR. CAMMARATA: From the time of onset of  
8 symptoms, is that what you're referring to?

9           DR. GREENBERGER: No. I'm talking about  
10 time to initiation of the intervention, the active  
11 treatment or something else.

12           DR. CAMMARATA: From the attack start. Is  
13 that --

14           DR. GREENBERGER: From the attack when it  
15 started to when -- because it seemed as if it made  
16 a difference in terms of the response.

17           DR. CAMMARATA: I have a summary slide  
18 showing the attack onset to the time of treatment.  
19 We'll get that up for you in a second.

20           Slide up, please. So this is, I believe, a  
21 summary of the data you're looking for. And here  
22 what we've done is we've looked at the phase 3

1 studies, all the patients that received icatibant,  
2 and then we also looked at the self-administration  
3 trial because that was one of the questions, what  
4 would be the time for patients that self-  
5 administered.

6 When we looked at the phase 3 study data  
7 where, as Dr. Riedl referred to, we have  
8 investigators ready, willing and able to dose these  
9 patients, from the attack onset to treatment, it  
10 was about almost 8 hours, 7.6 hours. And when you  
11 looked from attack onset to the almost complete  
12 symptom relief to where all those VAS scores were  
13 less than 10, it was almost 19 hours.

14 When we looked at the self-administration  
15 trial, patients, since they had access to the  
16 syringe, were able to dose more quickly. So their  
17 time of attack onset to treatment was 4 and a half  
18 hours, and then their time from attack onset to  
19 almost complete symptom relief was 14 hours. So  
20 when you look at the entire breadth of the attack,  
21 it was shorter.

22 The actual time from dose to the time of

1 symptom relief, whether you looked at the composite  
2 score or the primary symptom score, was the same  
3 whether or not they gave it through a physician or  
4 from the patient. It was consistently two hours.

5 DR. GREENBERGER: Do you have that for  
6 FAST-1?

7 DR. CAMMARATA: I do have that data for  
8 FAST-1. I have the data. I can show you for all  
9 three studies.

10 Slide up, please. When we look at the  
11 individual studies, FAST-1 and FAST-2 versus  
12 FAST-3, you can see the mean time for FAST-1 and  
13 FAST-2 are 12 and then 10 hours from the attack  
14 onset to the time they receive treatment. And then  
15 the FAST-3 was 7 hours.

16 DR. KRISHNAN: Great. I think just to give  
17 everybody a point of order here, we're about four  
18 or five more committee members who wanted to ask  
19 questions, and we're nearing the 10:30 timeline for  
20 taking a break. In talking with Dr. Khuc, we  
21 decided perhaps we'll go five minutes into the  
22 break, we'll take a break. And then for those of

1 you who had questions that we don't get to, we will  
2 allow you to proceed during the discussion time,  
3 and we'll try to keep order, if that's acceptable  
4 to the committee members.

5 [No verbal response.]

6 DR. KRISHNAN: Okay. Hearing no at least  
7 extreme objection, we'll proceed with that plan.

8 I think Dr. Portnoy, I think you had a  
9 question next.

10 DR. PORTNOY: Obviously, this is a product  
11 that's going to be most effective if it's injected  
12 by the patient, and that's how it's designed. I  
13 was wondering, is this planned to be developed as  
14 an auto-injector or as a syringe with a needle?  
15 Does it need to be injected subcutaneously or  
16 intramuscularly? What about the stability, the  
17 temperature stability? What is the -- how long  
18 does it last before it expires?

19 I'm interested in those types of questions  
20 because that will be an important aspect of the  
21 product.

22 DR. CAMMARATA: So you're asking packaging.

1 It is designed as a sub-Q injection. I'll ask Jim  
2 Weston to stand up and talk a little bit about the  
3 packaging and stability.

4 DR. WESTON: Jim Weston, senior director,  
5 regulatory affairs at Shire.

6 Slide up, please. This shows the actual  
7 primary container itself. So it's a prefilled  
8 sterilized syringe with a needle that goes along  
9 with it. And then it's packaged into a secondary  
10 package which provides protection but also provides  
11 ease of access to it.

12 Regarding your question about stability, the  
13 product is labeled to be stored at 25 degrees  
14 Centigrade, approximately 77 degrees Fahrenheit or  
15 less, and should not be frozen. So it's a very  
16 broad range of stability of use of the product.

17 DR. PORTNOY: Of course, if they keep it in  
18 their car or walk around with it, it's likely to be  
19 exposed to different extremes of temperature and  
20 sunlight and so on. Is there any tolerance of  
21 that? Because, otherwise, they're not going to be  
22 able to carry it around with them?

1 DR. WESTON: Sure; two aspects to it. One  
2 is, as you recall the range, it can be stored from  
3 zero up to 25. If someone were to go into an area,  
4 let's say it would be an elevated  
5 temperature -- for example, they're going to take  
6 it to a beach or something like that -- we'd  
7 recommend they keep it in the cooler, keep it  
8 refrigerated; or if they live in a hot climate,  
9 again, we would recommend they keep it in a  
10 refrigerator for a period of time. So in aspects,  
11 we cover a broad range to be able to use that.

12 DR. KRISHNAN: Dr. Jacoby.

13 DR. JACOBY: Dr. Greenberger already  
14 discussed the question.

15 DR. KRISHNAN: Okay. Dr. Mauger, I think  
16 you're next.

17 DR. MAUGER: I had a couple of questions.  
18 I'll do them one at a time, if that's okay. First  
19 off had to do with your assessment of the primary  
20 outcome. According to protocol, the patients were  
21 going to be responding to the VAS at 12,  
22 24 -- well, there were a number of measurements

1 before 12 hours, but then there were three  
2 measurements at 12, 24 and 48 hours.

3 The results that you've shown on the Kaplan-  
4 Meier indicate that there are a number of events  
5 occurring between 12 and 24 and between 24 and 48  
6 hours. Why is that?

7 DR. CAMMARATA: Some of that -- actually,  
8 I'll ask Dr. Amato to comment on that because it's  
9 the timing on when patients came to the clinic and  
10 how the data was collected.

11 DR. AMATO: David Amato, senior director of  
12 biometrics at Shire HGT. The reason for that is  
13 that when we talk about 24 hours, it's really the  
14 day 2 morning assessment. So it may not occur  
15 exactly at 12 and 24 hours, depending on what time  
16 they came into the clinic.

17 DR. MAUGER: So what might drive them coming  
18 into the clinic would be them feeling better or  
19 feeling worse? I guess I'm wondering whether the  
20 timing of the measurement might be correlated with  
21 their current status.

22 DR. AMATO: So if they came in, in the

1 evening, for example, let's say at 9:00, then 12  
2 hours later would be 9:00 in the morning. It'd be  
3 pretty close to their morning assessment.

4 DR. CAMMARATA: Actually, they had to come  
5 back into the clinic for assessment.

6 DR. AMATO: So it's really all about the  
7 timing. It was day 2 morning, not necessarily the  
8 24-hour assessment.

9 DR. MAUGER: I had a follow-up question  
10 about the assessment of adverse events in the open  
11 label self-administration study. You reported  
12 23 percent of patients having HAE as an adverse  
13 event. That's what they were being treated for.  
14 So was there a misunderstanding about what they  
15 were -- that's either gross underreporting or there  
16 was some misunderstanding about how they were  
17 supposed to report adverse events.

18 DR. CAMMARATA: In the trials, patients and  
19 physicians were told to specifically -- if they had  
20 any change in symptoms, so they come in with HAE,  
21 they get dosed. If they had any change in symptoms  
22 and it could be minimal changes in symptoms, they

1 were told to report it as an adverse event. So  
2 that could be a little blip up in my skin pain or  
3 abdominal pain. And most of the patients did  
4 actually -- didn't use any -- very few used any  
5 medication for it, but that was a requirement of  
6 the protocol, to capture any changes in symptoms as  
7 an adverse event.

8 DR. MAUGER: Last question. You talked at  
9 some points about the importance of work missed and  
10 school missed.

11 Do you have data on that from your trial as  
12 to what --

13 DR. CAMMARATA: No, we did not collect any  
14 data regarding quality of life.

15 DR. KRISHNAN: Okay. I think we are roughly  
16 five minutes into the break, so we will now take a  
17 10-minute rather than 15-minute break. We will  
18 reconvene again in this ballroom at 10:45 a.m.

19 Panel members, please remember that there  
20 should be no discussion of the issue at hand during  
21 the break amongst yourselves or any members of the  
22 audience. Thank you.

1 (Whereupon, a recess was taken.)

2 DR. KRISHNAN: I think we're going to get  
3 started again. It's about 10:45, if you want to  
4 take your seat.

5 So I'd like to begin with the next part of  
6 the presentation. We will now proceed with the FDA  
7 presentations. The questions, we're going to do  
8 them in the afternoon because we need to keep to  
9 the schedule. And for those of you that were  
10 unable to ask questions during this period, we'll  
11 have an opportunity during the afternoon.

12 **FDA Presentation - Brian Porter**

13 DR. PORTER: Good morning. My name is Brian  
14 Porter, and I'm the primary clinical reviewer for  
15 this application. I'm board certified in internal  
16 medicine and pediatrics and allergy and immunology.

17 Today, I will be presenting for you the  
18 chronology of the division's review of the  
19 icatibant development program as well as our  
20 overall interpretation of the efficacy and safety  
21 data submitted in support of the proposed  
22 indication. To begin, I will review the original

1        icatibant NDA submission which comprised the first  
2        review cycle for this application, including a  
3        summary of the key clinical trials, endpoint  
4        validation studies, and phase 3 efficacy findings  
5        from FAST-1 and FAST-2, which led to the issuance  
6        of a not approvable action letter by the agency.

7                I will then describe the subsequent steps  
8        the applicant took to present additional data in  
9        support of icatibant, including a request for a  
10       special protocol assessment for the third and final  
11       pivotal efficacy trial, FAST-3, as well as the  
12       components of the recent complete response  
13       submission by the applicant, which constitutes the  
14       second review cycle for this application.

15                The phase 3 efficacy findings from this  
16       complete response will be presented by Dr. Joan  
17       Buenconsejo of the division of biometrics.  
18       Following Dr. Buenconsejo's presentation, I will  
19       conclude by presenting the pooled safety findings  
20       of the icatibant phase 3 program, including an  
21       assessment of icatibant self-administration.

22                To place our discussion of icatibant

1 efficacy data into context, I would ask the  
2 committee members to again reflect on the pertinent  
3 question posed by the division. Do the data  
4 provide substantial and convincing evidence of a  
5 clinically meaningful benefit for icatibant in the  
6 treatment of acute attacks of HAE? Points the  
7 division would appreciate the committee members to  
8 consider in particular include the clinical  
9 relevance of efficacy results based on visual  
10 analog scale assessments as well as the overall  
11 adequacy of the icatibant efficacy database with  
12 respect to the proposed indication for the  
13 treatment of acute HAE attacks.

14 This table summarizes the key phase 2 and 3  
15 clinical trials conducted in adults with HAE which  
16 comprised the original icatibant development  
17 program that was submitted for review with the  
18 original NDA. Not shown here are several phase 1  
19 clinical pharmacology trials of icatibant in  
20 healthy adults, which I will not describe further  
21 in this presentation.

22 Rather, I would like to draw your focus

1 first to Study 2101, an open label, phase 2, proof  
2 of concept trial evaluating single doses of  
3 icatibant at a limited number of IV and  
4 subcutaneous dose levels as acute treatment for  
5 moderate to severe cutaneous or abdominal HAE  
6 attacks. In addition to characterizing the  
7 clinical pharmacology of icatibant in HAE patients,  
8 this trial also generated limited dose ranging  
9 information in the form of both clinical efficacy  
10 and safety data at each dose level, including the  
11 30-milligram subcutaneous dose, which was the dose  
12 ultimately studied in phase 3 clinical trials.

13 The original icatibant phase 3 program  
14 consisted of two larger and similarly designed  
15 randomized double-blind control trials which  
16 compared the efficacy and safety of a single dose  
17 of either 30 milligrams of subcutaneously  
18 administered icatibant versus either a placebo  
19 control in FAST-1 or a tranexamic acid control arm  
20 with double dummy placebo injections in FAST-2.

21 These randomized treatments were  
22 administered for the subjects first on-study

1 moderate to severe acute cutaneous or abdominal HAE  
2 attack and were followed by a 14-day observation  
3 period for adverse reactions. Each of these trials  
4 was also followed by a 24-week open label extension  
5 phase in which all subsequent HAE attacks were  
6 treated with up to three doses of icatibant over a  
7 24-hour period as needed.

8 From the limited dose ranging information  
9 available from phase 2, the time to self-reported  
10 symptom relief onset appeared relatively rapid with  
11 subcutaneous dosing, approximately 30 minutes. In  
12 addition, efficacy results were similar for the  
13 30-milligram subcutaneous dose and the highest  
14 intravenous dose tested of 0.8 milligrams per  
15 kilogram, while the higher 45-milligram  
16 subcutaneous dose did not appear to offer any added  
17 benefit over the 30-milligram dose.

18 Of note, the doses and dose regimens of  
19 icatibant evaluated in this limited dose selection  
20 program were largely determined mechanistically by  
21 the estimated levels of bradykinin accumulation  
22 expected during acute HAE attacks as well as data

1 generated from an intravenous bradykinin challenge  
2 model in healthy adults that estimated the exposure  
3 of icatibant required to inhibit these elevated  
4 bradykinin levels.

5           The icatibant development program utilized a  
6 novel primary efficacy endpoint for the proposed  
7 indication; that being, post-dosing time to onset  
8 of primary symptom relief based on self-reported  
9 symptom ratings using a visual analog scale or VAS.  
10 This instrument is 100-millimeter line anchored by  
11 the extremes of no symptom at the starting point of  
12 zero millimeters versus the worst possible symptom  
13 at the opposite end of 100 millimeters, which the  
14 subject uses to graphically represent the intensity  
15 of the symptom based on where along the scale the  
16 VAS is marked.

17           While the VAS has been widely used as a pain  
18 assessment tool in clinical research, its proposed  
19 use to assess individual symptom domains of acute  
20 HAE attacks was novel. As specified in the  
21 protocols for these phase 3 trials, the time to  
22 onset of primary symptom relief was defined as the

1 time post-dosing to the first of three consecutive  
2 self-reported VAS symptom ratings that fell to the  
3 right and below a line defined by this equation,  
4 which is a function of the patient's baseline  
5 pretreatment VAS score.

6           Given the novel use of the VAS in this  
7 manner, the division noted its lack of validation  
8 as an efficacy measure in HAE. Thus, included in  
9 the original NDA submission was Study 4102, an  
10 observational, noninterventional validation study  
11 of this patient-reported outcome measure conducted  
12 in 80 adults with HAE. In this study, subjects  
13 provided self-ratings of their HAE symptoms during  
14 acute attacks using both the VAS as well as the  
15 Verbal Descriptor Scale, a five-point rating scale  
16 of symptom severity which the applicant designated  
17 as a comparative gold standard for evaluating  
18 symptom change over time.

19           Through correlative analysis, the applicant  
20 proposed a minimum clinically significant  
21 difference in VAS rating of 9 millimeters on the  
22 100-millimeter scale. In addition to Study 4102,

1 the sponsor also submitted studies to characterize  
2 the face, content and clinical validity of the VAS.  
3 While collectively these studies were consistent  
4 with agency guidance on development programs for  
5 patient-reported outcome measures, the division was  
6 cognizant of the lack of prior regulatory  
7 experience with VAS-based endpoints in HAE clinical  
8 programs as well as the novel nature of the VAS  
9 when used in this manner. Therefore, I would again  
10 ask the committee members to reflect on the  
11 clinical relevance of the icatibant program's  
12 VAS-based phase 3 efficacy findings.

13 The applicant has already summarized details  
14 regarding the demographic analysis of the icatibant  
15 phase 3 program. While the individual treatment  
16 groups within both FAST-1 and FAST-2 were generally  
17 well-balanced and comparable, the following points  
18 regarding the phase 3 efficacy database are  
19 noteworthy.

20 First, despite there being no gender  
21 predominance in this autosomal dominance disorder,  
22 the majority of trial participants were female. In

1 addition, nearly the entire study population was  
2 Caucasian, which raises potential concerns as to  
3 the generalizability of study findings to other  
4 ethnic groups.

5           Although HAE attacks at all anatomic sites  
6 were assessed in the clinical program, FAST-3 had a  
7 greater proportion of subjects with cutaneous  
8 versus abdominal HAE attacks. Of note, however,  
9 there were relatively few discontinuations within  
10 any given study arm, from zero to 3, which suggests  
11 that dropout rates did not bias trial results.

12           This table depicts the primary efficacy  
13 findings from each of the pivotal phase 3 efficacy  
14 trials; namely, the median time to onset of primary  
15 symptom relief. As shown, time to symptom relief  
16 onset was only 2 to 2 and a half hours for the  
17 icatibant treatment arms in the two trials, whereas  
18 tranexamic acid recipients in FAST-2 demonstrated  
19 the statistically greater lag time of 12 hours. In  
20 contrast, placebo recipients in FAST-1 had a median  
21 time of just over 4 and a half hours from dosing to  
22 symptom relief onset, which compared to a time of

1 2.5 hours in the icatibant treatment arm was  
2 nonsignificant.

3 In turn, only FAST-2 demonstrated a  
4 statistically significant treatment effect of  
5 icatibant. However, the interpretation of this  
6 finding was difficult given that tranexamic acid is  
7 not approved for treatment of acute HAE attacks in  
8 the United States. In turn, its effects on HAE  
9 symptomatology have not been fully characterized,  
10 and the theoretical risks exist of this agent to  
11 potentially worsen HAE symptoms during an acute  
12 attack, thereby artifactually magnifying any  
13 favorable treatment effect of icatibant in this  
14 parallel group design.

15 Moreover, when time to onset of primary  
16 symptom relief were stratified by HAE attack  
17 location into either cutaneous or abdominal  
18 attacks, in contrast to FAST-2, FAST-1 again failed  
19 to demonstrate any clinically significant effect of  
20 icatibant despite the placebo recipients in FAST-1  
21 having a median lag time for cutaneous symptom  
22 relief that was nearly three times higher than in

1       icatibant recipients.

2               Thus, given this range of inconsistent  
3 efficacy results in these two original pivotal  
4 phase 3 trials, on April 23rd, 2008, the agency  
5 issued a not approvable action letter to the  
6 application which cited several key clinical  
7 deficiencies in the icatibant development program.

8               First and foremost, the applicant had failed  
9 in this initial review cycle to provide substantial  
10 evidence of the safety and efficacy of icatibant  
11 for the proposed indication. This was particularly  
12 reflected in the nonsignificant study findings of  
13 FAST-1. Moreover, although a significant treatment  
14 effect favoring icatibant was evident in FAST-2,  
15 given the uncertainty of tranexamic acid as an  
16 appropriate comparator agent in this trial, these  
17 statistically significant findings were not  
18 considered to be convincing evidence of the  
19 effectiveness of icatibant for the treatment of  
20 acute HAE attacks.

21               Secondarily, persistent concerns over the  
22 validity of the VAS-based primary efficacy endpoint

1 were also noted. In addition, further data were  
2 requested in support of the safety of icatibant for  
3 self-administration by non-healthcare workers in  
4 non-clinical settings; in other words, self-dosing  
5 at home. And further definition of dose selection  
6 was requested in a sufficient number of patients  
7 based either on a clinical endpoint or other  
8 validated and related biomarkers.

9           Following issuance of the not approvable  
10 action letter, the division had several  
11 interactions with the applicant in furtherance of  
12 the icatibant development program. This included  
13 an end-of-review meeting on December 15th, 2008  
14 during which the division recommended that if the  
15 applicant were to undertake additional efficacy  
16 trials, the same primary endpoint should be  
17 utilized as for FAST-1 and FAST-2 in order to  
18 facilitate cross-trial comparisons; namely, time to  
19 primary symptom relief onset.

20           In addition, however, the division also  
21 recommended that the applicant explore composite  
22 HAE symptom scores. Such composite efficacy

1 measures may be of greater clinical relevance with  
2 respect to HAE attacks, which often present with a  
3 symptom complex as opposed to a single predominant  
4 symptom.

5 In turn, the applicant submitted a request  
6 for special protocol assessment on February 13th,  
7 2009 in order to seek concurrence from the agency  
8 on the design specifics of a third pivotal  
9 icatibant efficacy trial. Known as FAST-3, this  
10 was another randomized double-blind, placebo-  
11 controlled trial similar in design to FAST-1 and  
12 FAST-2. In contrast, however, FAST-3 utilized as  
13 its primary efficacy endpoint time to symptom  
14 relief onset based on a composite three component  
15 symptom score known as VAS-3, which was the average  
16 of individual VAS ratings for three major self-  
17 reported HAE symptom domains: abdominal pain, skin  
18 pain and skin swelling.

19 Although the division was generally  
20 supportive of the overall trial design of FAST-3,  
21 given the novelty of the proposed primary endpoint  
22 and the lack of regulatory experience with

1 VAS-based outcome measures in HAE clinical  
2 programs, the agency issued a no agreement SPA  
3 letter on April 2nd, 2009 in response to the  
4 proposed special protocol assessment.

5           Ultimately, the applicant conducted FAST-3  
6 as originally proposed, enrolling its first subject  
7 in July of 2009, which was three months prior to  
8 the agency's approval of C1 esterase inhibitor  
9 replacement therapy for the treatment of acute HAE  
10 attacks and five months' prior to the approval of  
11 ecallantide for this same indication.

12           On February 25th, 2011, the applicant  
13 submitted for review a complete response for  
14 icatibant, which now constitutes the division's  
15 second review cycle for this application. In order  
16 to address the clinical deficiencies cited in the  
17 not approvable action letter, this complete  
18 response contains the following elements.

19           As additional safety and efficacy data for  
20 icatibant, findings from FAST-3, the third pivotal  
21 phase 3 trial, are presented in full. To establish  
22 the safety and effectiveness of icatibant self-

1 administration, an additional phase 3B trial has  
2 also been reported, referred to as EASSI by the  
3 applicant and also known as FAST-4 as referenced in  
4 the agency's clinical briefing document.

5           Finally, to provide further justification of  
6 dose selection, an analysis of population PK data  
7 as well as pharmacokinetic/pharmacodynamic modeling  
8 data were newly compiled from the existing PK  
9 database across all trials along with study reports  
10 for two new clinical pharmacology trials, a  
11 thorough QT safety study and a PK analysis of  
12 repeated subcutaneous icatibant dosing in healthy  
13 adults, neither of which I will be discussing in  
14 this presentation, but which I would refer you to  
15 the agency's briefing document for further details.

16           Thus, the icatibant complete response  
17 consisted to two new phase 3 trials, FAST-3 and  
18 FAST-4 or EASSI, the designs of which are  
19 summarized here. As you can see, FAST-3 was of  
20 similar design to FAST-1 as a randomized, double-  
21 blind, placebo-control, single-dose trial. In  
22 contrast, EASSI utilized an open label design in

1 which a total of 56 icatibant-experienced subjects  
2 self-injected a single dose of icatibant at home  
3 for their first qualifying on-study HAE attack. A  
4 portion of these subjects were initially  
5 icatibant-naive at the time of enrollment and had  
6 their initial on-study HAE attack treated with  
7 icatibant administered by a healthcare worker in  
8 the clinic. After this, they were eligible to  
9 self-administer a single icatibant dose for their  
10 next acute HAE attack.

11           Although data have only been reported for 56  
12 subjects in this trial to date, a total of 151  
13 subjects were enrolled. In turn, the applicant  
14 states that the trial is ongoing with the 95  
15 subjects who have not yet self-treated remaining in  
16 the trial until either they self-treat or the trial  
17 is closed.

18           As the icatibant complete response presents  
19 data from these new phase 3 trials within the  
20 context of data from the original phase 3 trials,  
21 FAST-1 and FAST-2, I would like to review the key  
22 elements of the phase 3 trial design prior to

1 Dr. Buenconsejo presenting the efficacy findings  
2 described in the complete response.

3 As has been discussed, the trial designs of  
4 FAST-1, FAST-2 and FAST-3 were all similar as  
5 randomized control, double-blind, parallel group,  
6 multi-center trials in adults 18 years of age and  
7 older with either Type 1 or Type 2 HAE. In turn,  
8 the demographic distribution of each trial was also  
9 similar.

10 The main difference then was in choice of  
11 treatment comparator with FAST-1 and the newly  
12 submitted FAST-3 both being placebo-controlled  
13 trials where as FAST-2 utilized an unapproved  
14 comparator control agent, tranexamic acid.

15 The randomized treatment phases of each of  
16 these trials consisted of a single dose of  
17 subcutaneously administered icatibant,  
18 30 milligrams, versus comparator treatment for the  
19 subject's first moderate to severe cutaneous and/or  
20 abdominal HAE attack. However, following a  
21 protocol amendment to FAST-3, the same randomized  
22 treatment was also given for the first mild to

1 moderate laryngeal HAE attack, whereas for FAST-1  
2 and FAST-2, all laryngeal attacks were treated with  
3 open label icatibant. For FAST-3, open label  
4 icatibant was only given for severe laryngeal  
5 attacks.

6 All three trials also included open label  
7 extension phases in which all willing subjects were  
8 automatically enrolled. During the extension  
9 phase, all subsequent HAE attacks were treated with  
10 up to three doses of icatibant as needed within a  
11 24-hour period. Subjects could receive open label  
12 treatment for any number of recurring HAE attacks  
13 experienced throughout the six-month extension  
14 phase.

15 At this point, I would like to turn the  
16 floor over to Dr. Joan Buenconsejo, mathematical  
17 statistician and team leader from the Division of  
18 Biometrics, who will discuss key aspects of the  
19 efficacy endpoints utilized in the phase 3 program,  
20 followed by a detailed presentation of the major  
21 primary and secondary phase 3 efficacy analyses  
22 included in the complete response.

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**FDA Presentation - Joan Buenconsejo**

DR. BUENCONSEJO: Thank you, Dr. Porter.

Good morning. My name is Joan Buenconsejo, and I'm the acting statistical team leader supporting the division. I'll be describing the primary endpoints and the efficacy results submitted in the complete response.

As you heard from Dr. Porter and Dr. Cammarata, there is a change in the definition of the primary endpoint in the FAST-3 trial. Instead of basing symptom relief on a prespecified reduction criteria in the VAS score for a single identified primary symptom like in FAST-1 and FAST-2, symptom relief is now based on a 50 percent reduction in a three-component -- meaning skin pain, skin swelling and abdominal pain -- composite VAS score in FAST-3.

In order to facilitate cross-comparisons, post hoc analyses were conducted for FAST-1 and FAST-2 by calculating and evaluating the three-component VAS endpoint. In addition, the primary endpoint, based on single primary symptom used in

1 FAST-1 and FAST-2, was also specified as key  
2 secondary for FAST-3. Most of the results I'll be  
3 presenting were already presented by Dr. Cammarata.

4 Because of the small sample size of the  
5 laryngeal patients, only non-laryngeal patients  
6 were included in the main efficacy analysis.

7 As noted, on the top, FAST-3 demonstrated  
8 statistical significant treatment difference in the  
9 time to onset of symptom relief based on a three-  
10 symptom composite VAS. Despite the very low  
11 p value generated by comparing the two groups in  
12 FAST-3, the placebo and icatibant responses are  
13 noteworthy.

14 Compared to FAST-1, the second line, the  
15 median time to onset of symptom relief for the  
16 placebo group is longer in FAST-3 while the median  
17 time to onset of symptom relief is essentially the  
18 same for the icatibant group, which is about two  
19 hours. There's also significant treatment  
20 difference in the time to onset of symptom relief,  
21 based on three-symptom composite VAS between  
22 icatibant and tranexamic acid, with median time to

1 onset of symptom relief for the icatibant group is  
2 also about two hours. Both analyses in FAST-1 and  
3 FAST-2 are post hoc.

4 Dr. Porter already presented the results for  
5 FAST-1 and FAST-2. The primary endpoint is based  
6 on a single primary symptom VAS score. The results  
7 from phase 3, which is on the top line, is added to  
8 the table. FAST-3 demonstrated statistical  
9 significant treatment difference in time to onset  
10 of symptom relief based on a single primary  
11 endpoint. This is one of the key secondary  
12 endpoints for FAST-3.

13 Like in the previous table, which was based  
14 on three-composite VAS score, the median time to  
15 onset of symptom relief for the placebo group is  
16 longer in FAST-3 compared to FAST-1, while the  
17 median time to onset of symptom relief is  
18 essentially the same for the icatibant group, which  
19 is, again, about two hours.

20 Although significant treatment effects were  
21 observed in FAST-2 and FAST-3 by anatomic site of  
22 HAE attack, larger treatment differences are

1 observed for the cutaneous subgroup, which includes  
2 skin pain and skin swelling. It appears that  
3 patients who experienced abdominal HAE attacks  
4 tended to have symptom relief faster compared to  
5 those who experienced cutaneous HAE attack.

6 Of note, there are more patients actually  
7 who experienced cutaneous attacks in FAST-3 and  
8 FAST-2 compared to the patients with abdominal  
9 attacks. However, the treatment differences were  
10 all in the same direction. So like the overall  
11 population, median time to onset of symptom relief  
12 is essentially shorter, about two hours for  
13 icatibant group compared to the comparator across  
14 all subgroups.

15 As stated earlier, only non-laryngeal  
16 patients were included in the main efficacy  
17 analysis, and only a small proportion of laryngeal  
18 patients were included in these trials. When  
19 examined, the efficacy findings for patients  
20 treated with icatibant were generally consistent  
21 with the non-laryngeal patients; that is, time to  
22 primary symptom relief was about two hours, time to

1 composite symptom relief was about two hours, and  
2 there is a progressive reduction in laryngeal  
3 symptoms.

4           The durability of response, defined as the  
5 proportion of patients who experienced primary  
6 symptom relief within eight hours of dosing for  
7 which symptom relief lasted for 24 hours, were also  
8 examined. Consistent with the primary endpoint  
9 analysis, a significant higher proportion of  
10 patients in the icatibant group were able to  
11 maintain symptom relief in the FAST-2 and FAST-3  
12 studies compared to the control group. And these  
13 were driven mostly by the large treatment  
14 difference among patients who experienced cutaneous  
15 attacks.

16           Because the division has concern over a  
17 proposed primary endpoint analysis based on VAS-3  
18 and key secondary analysis based on the primary  
19 symptom VAS, we examined the treatment effects on  
20 secondary endpoints like the use of rescue and  
21 clinical global assessments, which are both  
22 unrelated, independent of the VAS score. The

1 number and percentage of subjects who received  
2 rescue before the onset of symptom relief, as well  
3 as any time during the HAE attack, which is within  
4 120 hours of the initial drug administration, were  
5 calculated and examined.

6           Meanwhile, the global investigator based  
7 assessment that took into account abdominal,  
8 cutaneous and laryngeal symptoms for all HAE  
9 attacks were graded on a five-point ordinal scale,  
10 ranging from zero, which is the absence of  
11 symptoms, to 4, which is very severe. None of  
12 these were adjusted for multiplicity. Therefore,  
13 only descriptive summaries are presented.

14           In all three studies, a higher proportion of  
15 control patients used rescue therapy prior to onset  
16 of symptom relief or any time during an attack. In  
17 all three studies, the distribution of cutaneous  
18 symptoms at various ratings at 4 hours post-dosing  
19 differed between icatibant recipients and the  
20 control subjects in FAST-2 and FAST-3 with a  
21 greater proportion of lower rating, which means  
22 good score, noted in the icatibant group. However,

1 this finding was not observed in FAST-1.

2 In addition, differences in global  
3 assessment of abdominal symptoms were less  
4 disparate between icatibant and the control group.  
5 This is consistent again with the general findings  
6 using the VAS symptom score. In addition,  
7 investigator assessments were also examined, and  
8 the results were also consistent.

9 In summary, statistically significant  
10 treatment effects were observed in one active  
11 control trial, which is the FAST-2, and one placebo  
12 controlled trial, which is FAST-3, for icatibant in  
13 the treatment of acute HAE attack. There's also  
14 sharp contrast in placebo response between FAST-1  
15 and FAST-3. Nonetheless, there is consistent  
16 evidence that median time to onset of symptom  
17 relief is about two hours when treated with  
18 icatibant regardless of how you define the primary  
19 endpoint. The results over the use of rescue or on  
20 the clinical global assessments are consistent with  
21 the findings using VAS scores.

22 Thank you. Now I'm turning over to

1 Dr. Porter, and he will be presenting the safety  
2 findings.

3 **FDA Presentation - Brian Porter**

4 DR. PORTER: Thank you, Joan.

5 I will now complete the FDA presentation by  
6 discussing the integrated safety analysis of the  
7 icatibant development program, including pooled  
8 safety findings from the pivotal phase 3 trials, as  
9 well as the results of the icatibant self-  
10 administration trial.

11 In order to place these safety findings into  
12 context, I would refer the committee members back  
13 to the pertinent question posed by the division.  
14 Has the safety of icatibant been adequately  
15 assessed for the treatment of acute attacks of HAE?  
16 In particular, I would encourage the committee  
17 members to consider the following points, which I  
18 will discuss in more detail: deaths, serious  
19 adverse events and subject withdrawals; common  
20 adverse events seen in the phase 3 program; local  
21 injection site reactions associated with icatibant  
22 dosing; and, finally, the safety of icatibant self-

1 administration by non-healthcare workers outside of  
2 the clinical setting.

3           Across all three phase 3 trials, the  
4 icatibant safety database consisted of data  
5 generated by the following safety assessments:  
6 adverse events categorized by the MedDRA  
7 classification system Version 8.1; clinical  
8 laboratory safety tests, including assessments of  
9 post-dosing immunogenicity; physical examination  
10 and vital sign assessments; 12-lead ECG  
11 evaluations; and a systematic assessment of local  
12 injection site reactions.

13           Data were compiled for a pooled safety  
14 population consisting of the intent-to-treat  
15 populations from the randomized treatment phases of  
16 each of the pivotal phase 3 trials consisting of  
17 113 icatibant recipients from FAST-1, FAST-2 and  
18 FAST-3, 38 tranexamic acid recipients from FAST-2,  
19 and 75 placebo recipients from FAST-1 and FAST-3.  
20 As has been discussed by the applicant, demographic  
21 data were similarly distributed among each of these  
22 three pooled treatment groups.

1           In addition to data collected during the  
2 randomized treatment phases of these trials, safety  
3 data were also compiled for the first five  
4 sequential icatibant-treated HAE attacks among all  
5 phase 3 subjects in which safety data were combined  
6 without regard to whether icatibant was delivered  
7 in randomized or open label fashion during the  
8 extension phase.

9           As shown here, icatibant exposure was  
10 extensive across the phase 3 program allowing for  
11 an assessment of data from subjects who received  
12 anywhere from zero to more than five recurrent  
13 doses of icatibant for sequential HAE attacks over  
14 time. With regard to dose exposure for any given  
15 HAE attack, as you can see, the vast majority of  
16 subjects received only a single dose of icatibant  
17 for their first or subsequent icatibant-treated HAE  
18 attacks. Approximately 10 percent of subjects  
19 received additional doses for a single HAE attack  
20 with a negligible number receiving the maximum of  
21 three injections permitted over a 24-hour period.

22           Thus, this safety database is less

1 informative with regard to larger overall icatibant  
2 doses for a single HAE attack as it is for  
3 recurrent intermittent dosing for multiple attacks  
4 over time.

5 In terms of major safety findings, there  
6 were no deaths reported in any icatibant  
7 recipients. A total of seven serious adverse  
8 events among five subjects were reported in the  
9 pooled phase 3 safety population, all of which were  
10 from FAST-2. These included two cases each of  
11 pregnancy, which by definition was considered a  
12 serious adverse event regardless of outcome and  
13 worsening or recurrent HAE symptoms, as well as  
14 single cases of viral gastroenteritis, hypertensive  
15 crisis, and cystitis.

16 Only two withdrawals of icatibant recipients  
17 were reported in the phase 3 safety population with  
18 the reason listed non-specifically as other and no  
19 further information provided to allow for an  
20 assessment of causality to study drug.

21 Of note, no hypersensitivity or anaphylactic  
22 reactions were reported in the icatibant

1 development program, while post-dosing anti-drug  
2 antibody formation was observed in only one  
3 icatibant recipient who also had equivalent  
4 pretreatment titers at baseline. Moreover, these  
5 titers were transient as this subject has several  
6 negative serum samples drawn at later time points.  
7 There was also no evidence of neutralizing activity  
8 as icatibant response times in this subject were  
9 maintained throughout the extension phase during  
10 subsequent HAE attacks.

11 Thus, hypersensitivity reactions and the  
12 development of anti-drug antibodies do not appear  
13 to be major safety risks with recurrent icatibant  
14 dosing, according to the phase 3 program.

15 Adverse events were divided into events  
16 reported during the acute treatment period within  
17 24 hours of study drug dosing as well as over the  
18 entire course of the 14-day post-dose observation  
19 period from day 1 through day 14. This table  
20 summarizes those adverse events occurring in at  
21 least 2 percent of icatibant recipients and at a  
22 greater rate with icatibant treatment versus either

1 group of control subjects.

2 As shown, the rates of these adverse events  
3 were low except for local injection site reactions  
4 seen in almost all icatibant recipients, which I  
5 will describe in more detail later, and worsening  
6 HAE symptomatology. Per protocol, any worsening or  
7 recurrent signs or symptoms of HAE were reported as  
8 adverse events if they occurred within 48 hours of  
9 study drug dosing. Worsening symptoms that  
10 occurred beyond this time frame were reported as  
11 new HAE attacks rather than as adverse events and  
12 were treated accordingly.

13 However, the applicant acknowledges that  
14 some individual investigators may have mistakenly  
15 reported as an adverse event new HAE attacks,  
16 leading to potential over-reporting of HAE as an  
17 adverse event. In addition, it is difficult to  
18 assign causality of such events as a consequence of  
19 study treatment as these manifestations overlap  
20 with the clinical presentation of the underlying  
21 HAE attack. Nonetheless, the rate of HAE adverse  
22 events was actually higher in placebo recipients

1 compared to icatibant recipients.

2 With regard to severe adverse events, except  
3 for severe local injection site reactions, which  
4 will be discussed separately, severe adverse events  
5 were consistently observed at higher rates in  
6 placebo recipients versus icatibant recipients with  
7 two exceptions, a single case of severe dyspepsia  
8 and a single case of severe headache, two  
9 conditions which were not observed at a severe  
10 level in any control subjects. Of note, however,  
11 dyspepsia was a rare adverse event with only one  
12 other non-severe case reported in a placebo  
13 recipient, while the overall rate of headaches of  
14 any severity level was lower in icatibant  
15 recipients compared to control subjects.

16 It is important to note that local injection  
17 site reactions were systematically assessed in the  
18 icatibant development program as a separate safety  
19 endpoint in every subject at multiple time points  
20 throughout the first 24 hours post-dosing. Per  
21 protocol, local injection site reactions were not  
22 required to be reported as adverse events unless

1 they met criteria as a serious adverse event. In  
2 addition, patient- and investigator-reported  
3 severity ratings of these reactions were based on  
4 size or extent, differing from the severity  
5 definitions used to categorize other adverse  
6 events.

7 Thus, although local injection site  
8 reactions were rarely reported as adverse events,  
9 the data indicate that such reactions occurred  
10 almost universally following icatibant  
11 administration. Specifically, injection site  
12 erythema occurred in 96 percent of icatibant  
13 recipients and was classified as severe in over  
14 25 percent of those cases. Other commonly observed  
15 injection site reactions included localized  
16 swelling and warmth.

17 Although localized site reactions were most  
18 often mild to moderate and were generally self-  
19 limited or required only minimal intervention,  
20 these phenomena were far more common in icatibant  
21 recipients compared to control subjects, which has  
22 implications for the tolerability profile of

1         icatibant as well as a possible impact on study  
2         drug blinding during the randomized treatment  
3         phases of these trials.

4                 Finally, with regard to the feasibility and  
5         appropriateness of icatibant self-administration,  
6         results from the open label uncontrolled EASSI  
7         trial indicate the time to symptom relief onset was  
8         similar following icatibant self-dosing, as seen  
9         with icatibant treatment in each of the pivotal  
10        phase 3 efficacy trials, whether assessed by  
11        primary VAS symptom ratings or the composite VAS-3  
12        symptom score.  However, again, EASSI was an  
13        uncontrolled trial with no comparator arm by which  
14        to gauge treatment effect.

15                Nonetheless, the adverse profile associated  
16        with icatibant self-administration was similar to  
17        that of the pooled phase 3 safety analysis with  
18        worsening or recurrent HAE being the most commonly  
19        reported adverse event in 23 percent of subjects  
20        and local injection site reactions again widely  
21        observed in nearly 90 percent of patients.

22                Thus, reflecting on the data we have

1 summarized in this presentation, it is noteworthy  
2 that FAST-1 failed to demonstrate a significant  
3 treatment effect of icatibant versus placebo,  
4 whereas a statistically significant effect favoring  
5 icatibant was observed in FAST-3. While a  
6 significant treatment effect was also observed with  
7 icatibant versus tranexamic acid in FAST-2, the  
8 interpretation of this result is complicated by the  
9 choice of an unapproved comparator agent with  
10 incompletely characterized effects on HAE symptoms.

11 Also, as just discussed, the safety and  
12 efficacy results of icatibant self-administration  
13 as observed in the EASSI trial were similar to  
14 those of the three pivotal phase 3 trials,  
15 including the nearly universal occurrence of local  
16 injection site reactions following icatibant  
17 administration, although these reactions were  
18 largely self-limited and required only minimal  
19 intervention.

20 At this point, I would like to conclude the  
21 FDA presentation and thank the committee members  
22 for your attention and thoughtful consideration of

1 the discussion points that we have presented to you  
2 today. Thank you.

3 **Clarifying Questions for FDA**

4 DR. KRISHNAN: Great. Thank you very much.

5 We'll now proceed -- we'll now ask committee  
6 members if they have questions for the FDA. I'd  
7 like to take this opportunity perhaps to begin with  
8 one question.

9 The primary endpoint for the FAST trials, as  
10 we've discussed, is based on the patient-reported  
11 outcome of the Visual Analog Scale. And, of  
12 course, patient-reported outcomes can be important  
13 and clinically meaningful, but the data you  
14 presented with local site reactions that is  
15 universal practically in those receiving drug, and  
16 although not universal in the placebo arm,  
17 certainly less common, suggests to me that there's  
18 huge risk of unmasking during the trial.

19 Wanted to ask the FDA about whether there  
20 are any concerns about this potential for unmasking  
21 as raising questions about the validity of the  
22 Visual Analog Scale for the primary efficacy

1 endpoint.

2 DR. LIMB: So you raise a valid concern, and  
3 that's something that we were certainly aware of,  
4 was this issue of potential unblinding with the  
5 nearly universal injection site reactions. I think  
6 the larger issue, though, is that hereditary  
7 angioedema is a very difficult disease to study in  
8 clinical trials, and looking at different possible  
9 endpoints, ultimately, you end up with some  
10 combination of patient-reported outcome. It was  
11 hard to avoid.

12 So I think it's a factor that we have had to  
13 take into consideration, and certainly, we ask you  
14 to do the same. We also ask that you consider the  
15 secondary endpoints as well. So I think rescue  
16 medication use in particular might be helpful in  
17 that regard.

18 DR. KRISHNAN: Great.

19 Other committee members have questions?  
20 Dr. Borish?

21 DR. BORISH: I had another question, but I  
22 did want to follow up on yours. And maybe the

1 people who can answer this are Dr. Lumry or Riedl.

2 Those of you who did the FAST-1 and 2  
3 studies with the near universal local reaction, did  
4 you, in fact, know who was getting the drug by the  
5 time you got to FAST-3? Either one of you, I'm  
6 just curious.

7 DR. KRISHNAN: Does a representative of the  
8 sponsor want to respond?

9 DR. LUMRY: Bill Lumry, private practice,  
10 Dallas, Texas.

11 Dr. Borish, would you repeat your question?  
12 I didn't quite get the gist of it.

13 DR. BORISH: With the near universal  
14 occurrence of a large local in the patients getting  
15 the drug and having done FAST-1 and FAST-2, when  
16 you got to FAST-3, did you in fact know, and did  
17 your office people in fact know, everybody who was  
18 getting the active agent by the time you got to  
19 FAST-3?

20 DR. LUMRY: We participated in FAST-1 and  
21 FAST-3. FAST-2 was the European trial. The  
22 injection site reactions were obvious both to site

1 personnel, as well as to the investigator, as well  
2 as to the patient. There were about 30 percent of  
3 patients who had reactions to the placebo  
4 injection. They varied a little bit in that they  
5 didn't last as long. There wasn't as much redness  
6 or complaint by the patient of stinging or itching.  
7 But there was that bit of unblinding that the  
8 administrator, the investigator, the patient were  
9 aware that they were having an injection site  
10 reaction. No comment was made to the patient that,  
11 oh, you got the real drug because you're having  
12 this reaction, but we were aware of the reaction  
13 and what it looked like.

14 DR. BORISH: And I appreciate Dr. Limb's  
15 remark and will accept that, but I suspect the  
16 patient who had a painful, swollen red arm for some  
17 duration might have speculated, "I bet that wasn't  
18 a placebo."

19 DR. LUMRY: The injections were given in the  
20 abdomen. They may well have suspected that. Not  
21 all of the patients that were treated in FAST-3 had  
22 received icatibant before. There were a few

1 patients who had been in FAST-1 that repeated in  
2 FAST-2, but there were a variety of patients who  
3 were treatment naive in FAST-3. Dr. Cammarata  
4 probably has that specific number, but there were  
5 some treatment-naive patients who hadn't been  
6 exposed before and seen the effect of icatibant on  
7 their skin.

8 DR. KRISHNAN: Let me just remind the  
9 committee members. The primary purpose of this  
10 section of the discussion is to get clarification  
11 from the FDA. Obviously, if there's some  
12 discussion that's directly relevant and perhaps the  
13 sponsor can answer, I think it's reasonable. But  
14 we want to limit our questions to FDA  
15 clarification.

16 I think the sponsor did want to make one  
17 other clarification comment related to this line of  
18 questioning; is that right?

19 DR. CAMMARATA: I think --

20 DR. KRISHNAN: I'm sorry. Do you want to  
21 take to the mic? And then I think we probably  
22 should try to stick with asking for clarification

1 of the FDA for this portion of the meeting.

2 DR. CAMMARATA: I think we agree that this  
3 is an important point, and I can show -- we do have  
4 analyses to look at this issue because, of course,  
5 everybody knew that this was a potential issue. So  
6 if you don't mind, I'd like to show a couple of the  
7 analyses that we did looking at this issue since I  
8 think everybody here is interested.

9 Would that be acceptable?

10 DR. KRISHNAN: I think that's acceptable.

11 DR. CAMMARATA: Okay. As you said, it's a  
12 difficult issue because everybody -- at least in  
13 the trials, the majority of patients had some type  
14 of injection site reaction, and they were aware  
15 that we were aware. So in the design of the  
16 trials, we were trying to do the best we can to  
17 make sure that patients were blinded and the  
18 physicians were blinded.

19 So this is only involving the first dose  
20 because that's the only dose that was randomized  
21 double-blind, so one dose. The packaging was  
22 blinded so when the physicians dosed, they had no

1 idea what they were giving, and the patients were  
2 unaware.

3 The patients aren't aware of what they  
4 received. They do sign an informed consent that  
5 talks about that there's a potential for injection  
6 site reaction, but it differs from patient to  
7 patient. As you saw, some patients have very mild  
8 reactions; some will have a lot of redness. It  
9 varies. But even 30 percent of the patients on  
10 placebo also had an injection site reaction.

11 So we did a number of analyses because we  
12 wanted to see if we can tease if this was an issue.  
13 So I have a series of three slides. First slide,  
14 so we said -- again, we like our Kaplan-Meier  
15 curve. It shows you every single patient. So what  
16 we said is let's take everybody who had an  
17 injection site reaction. If they're on placebo,  
18 because they had an injection reaction, maybe they  
19 thought they got drug. So did that make a  
20 difference for the placebo patients who did not get  
21 injection site reactions? So you see a similarity  
22 of the KMs for both these populations of patients,

1 so placebo group with the reaction; placebo group,  
2 no reaction.

3 Second analysis, we said let's look at the  
4 time to onset of symptom relief for everybody who  
5 had an injection site reaction. So the yellow line  
6 is the icatibant patients, these are all the  
7 icatibant patients who had an injection site  
8 reaction, and the median time was two hours. We  
9 said look at all the placebo patients who had an  
10 injection site reaction. Their median time was six  
11 hours.

12 Then we said let's make this even more  
13 stringent. When we look at this endpoint of time  
14 to onset of symptom relief, we required, from their  
15 most severe symptoms, a 50 percent drop. Let's  
16 make it 70 percent. We're going to really make  
17 this a big treatment effect. So this is the  
18 analysis of time to onset of symptom relief  
19 requiring now a 70 percent improvement from their  
20 baseline to have that endpoint. So when we looked  
21 at the data for icatibant, its median time was  
22 3.6 hours, for placebo, it was almost 21 hours, and

1 for the tranexamic acid, it was 26 hours.

2 So we understand the question that folks had  
3 regarding this, but given the fact that this was  
4 that single dose and that we see again the  
5 consistent result for icatibant, even in these  
6 analyses, we feel that the icatibant does have a  
7 clear effect for those patients who have HAE.

8 DR. KRISHNAN: I'm sorry. Just to get  
9 clarification on this slide, does this include only  
10 the participants who had injection site reaction or  
11 all participants?

12 DR. CAMMARATA: I believe it's in all  
13 patients; all patients.

14 DR. KRISHNAN: So it doesn't directly get  
15 at, I think, the other point we've been talking  
16 about.

17 DR. CAMMARATA: Yes. The number between the  
18 all, I think it's only a couple patients  
19 difference, actually, if you take them out of the  
20 icatibant group. But you're looking at the other  
21 issue.

22 DR. KRISHNAN: Placebo groups, yes.

1           Okay. I think we should probably go on to  
2 some other questions, and we may come back to this  
3 if there's interest among the committee members.

4           So on the list Dr. Khuc has, I think,  
5 Dr. Foggs, I think you're next.

6           DR. FOGGS: Yes. I would like the FDA to  
7 comment on the utility of the secondary endpoint  
8 independent of VAS when you take into consideration  
9 that the Kaplan-Meier curves for the FAST-1 and  
10 FAST-3 time to almost complete symptom relief could  
11 have arbitrarily been placed at 70 to 100 hours and  
12 that there was ongoing resolution of the symptoms  
13 for both placebo as well as for the receptor  
14 blocker antagonist.

15           So to that extent, my question is, should  
16 there be a specific criteria set for determining  
17 when the cut point should be as opposed to what  
18 appears to be an arbitrarily chosen 48 hours?

19           DR. LIMB: So I guess the time to almost  
20 complete symptom relief was not independent of the  
21 VAS. So I'll just clarify that first point. So it  
22 is another variant of the VAS measure. And if I

1 remember correctly, I believe it's when the VAS  
2 fell below 10 milliliters on the 100 milliliter  
3 scale.

4 As to the end -- as far as how far they  
5 followed patients out, the trial was done looking  
6 out to 48 hours, and then there was additional  
7 follow-up after that point. The assessments that  
8 were done at later time points, though, were not as  
9 rigorous. And so I think there is some argument  
10 that maybe the 48-hour time point is somewhat  
11 arbitrary, but I think from the experience that  
12 we've had with hereditary angioedema, most of the  
13 acute attack is occurring within that first 24 to  
14 48 hours.

15 I don't know if that answers your question  
16 fully.

17 DR. FOGGS: It answers my question. My  
18 concern is that what will be defined as an  
19 exacerbation may actually be a recurrence based  
20 upon where you set the time frame so that -- the  
21 comment has already been made that there is  
22 heterogeneity and variability in expression of this

1 disease based upon variable penetrants and variable  
2 expressivity in association with this autosomal  
3 dominant inheritance mechanism.

4 To that extent, I think that the outcomes  
5 are going to be influenced by where this cut point  
6 is established. And to that extent, that would  
7 result in an interpretation of the data that could  
8 be called into question based on what appears to me  
9 to still seem to be a relatively arbitrary time  
10 frame for 48 hours.

11 I'd like to see what the data looks like  
12 when the time frame for the cut point is altered  
13 forwards or backwards to see whether or not the  
14 outcomes are impacted substantially.

15 DR. KRISHNAN: So maybe what we can do in  
16 the subsequent discussion period, we could ask the  
17 sponsor to look to other time points, but I think  
18 at this point, let me ask that we move to the next  
19 committee member.

20 Dr. Posner, I believe you had been long  
21 raising your hand, so it's now your turn.

22 DR. POSNER: That's fine. And these are

1 just for the FDA panel. I have others for the  
2 applicant.

3 One of the things that -- I wonder if you're  
4 troubled. I know you mentioned it was the  
5 100 percent Caucasian makeup of the cohort. And  
6 particularly with the QT lengthening side effect, I  
7 know in their work, they showed there was nothing  
8 significant in the way of arrhythmias. But in  
9 Asian-Americans, African-Americans, there's a  
10 larger impact of QT increase on a regular formation  
11 and reentry arrhythmias. And I wondered whether we  
12 can accept just 100 percent Caucasian cohort and  
13 say the QT is not significant without looking at  
14 groups that do have significant QT changes.

15 DR. LIMB: So I think the question that you  
16 bring up about the representation of other ethnic  
17 groups is an important one. I think because this  
18 is an orphan indication, we are limited in the  
19 population that's available for study. And as was  
20 previously mentioned by the company, the database  
21 that they're showing here today is actually a  
22 fairly large one given the indication. So while I

1 think we would always like to see additional data  
2 in subgroups, that being said, the total numbers  
3 that are shown here are actually -- they are  
4 probably about as well as we could expect given the  
5 rarity of the disease.

6           Regarding the QT issue, the company has done  
7 a designated thorough QT study, which indicates  
8 that there is no effect on the QT -- the concern of  
9 QT prolongation. That is a fairly rigorous study.  
10 Now, it could be that if the drug goes out into  
11 other ethnic groups, there's always the possibility  
12 that a new safety signal might arise. But based on  
13 the best available information, we do not have a  
14 current concern about QT prolongation.

15           DR. POSNER: The reason I question that is  
16 the question of bradykinin's effect on potassium  
17 channels and that effect on QT, and the possibility  
18 that the drug is a partial agonist rather than a  
19 complete blocker.

20           DR. CHOWDHURY: I'm Dr. Chowdhury. Just a  
21 comment on the QT effect, this is interesting and  
22 an important safety aspect to look at. And

1 Dr. Limb just mentioned that there was a thorough  
2 QT study done.

3 Just a sort of background on the thorough QT  
4 study, these studies are pretty carefully designed  
5 and pretty carefully done with active controls in  
6 place using a higher dose. And these protocols are  
7 pretty thorough, and the whole concept of a  
8 thorough QT study was to have led by a larger body,  
9 which is the ICH, actually, ICH guidelines on how  
10 to do a thorough QT study, and that was followed.  
11 And those are pretty rigorous testing. And that's  
12 the best that one can achieve assessing the QT  
13 effect, and this was done.

14 Again, the rare possibility of some rare  
15 genetic makeup, getting the patients and having a  
16 QT effect is a possibility. But the current  
17 standards of testing that needs to be done were  
18 done. Thank you.

19 DR. KRISHNAN: Okay. I think Dr. Portnoy,  
20 you had a question.

21 DR. PORTNOY: Yes. I was interested in the  
22 initial pharmacokinetics/pharmacodynamics data and

1       how the dosing was selected. My understanding is  
2       that this was done using healthy adults and in a  
3       variety of dosing ranges with bradykinin. But my  
4       question is whether patients with hereditary  
5       angioedema might have altered responsiveness to  
6       this, given the fact that they have repeated  
7       episodes of increased bradykinin exposure.

8               Does that modify up or down, regulate the  
9       bradykinin receptor and responsiveness to that, and  
10      was that something that the FDA might have been  
11      concerned about in terms of selecting the dose?

12             DR. LIMB: So I'll take an initial stab at  
13      the issue of dose selection, and perhaps the  
14      applicant can speak more about the actual PK data  
15      that you are inquiring about.

16             So I think dose selection for this product  
17      was a combination of the healthy adult challenge  
18      models that you mentioned as well as information  
19      that was obtained from a proof-of-concept trial  
20      that was done in HAE patients. And in that proof-  
21      of-concept trial, it appeared that 30 milligrams of  
22      icatibant had an effect that was as good, if not

1 better, than higher doses. And so that combined  
2 with the bradykinin challenge model was the basis  
3 for selecting the 30-milligram dose.

4 I think ultimately when we consider whether  
5 dose selection is appropriate, we have to look at  
6 the clinical trials that were done. And when we  
7 look at the phase 3 trials, there appears to be a  
8 fairly consistent demonstration of efficacy to  
9 support the 30-milligram dose.

10 I think the other aspect that we can look at  
11 is the frequency of patients who required a second  
12 dose -- because they were permitted to have a  
13 second dose within six hours if they had relapse or  
14 persistent symptoms -- was actually quite small,  
15 which would suggest to us that 30 milligrams seemed  
16 to be appropriate at least for the majority of  
17 patients.

18 DR. KRISHNAN: Okay. Great.

19 Dr. Platts-Mills.

20 DR. PLATTS-MILLS: Thank you.

21 Dr. Limb, following the initial submission,  
22 the FDA evaluated the design of the third study and

1 approved VAS, or actually recommended VAS as the  
2 correct method to evaluate it; is that correct?

3 DR. LIMB: So there was some discussion in  
4 Dr. Porter's presentation about special protocol  
5 assessment and the discussion that happened around  
6 it, and the SPA process is a binding process. And  
7 the agency felt at the time that given our relative  
8 lack of regulatory experience with HAE and HAE  
9 trials, that we couldn't enter a binding agreement.

10 But that being said, we felt that the  
11 general idea for FAST-3, including the selection of  
12 the primary endpoint based on the VAS, was  
13 reasonable with the idea that we would be taking it  
14 to a public forum like this one and asking all of  
15 you to discuss the VAS and whether you feel the  
16 results are clinically meaningful.

17 DR. PLATTS-MILLS: In addition, there was  
18 implied criticism of the change to a three-point  
19 VAS, the VAS-3. There was a letter from the FDA  
20 implying criticism of the VAS-3. So the question  
21 would be if you analyzed the data on FAST-3 using  
22 whatever criteria, would there be any difference in

1 the significance?

2 DR. LIMB: So perhaps "criticism" of that  
3 VAS-3 is too strong. I think we had concerns  
4 because the first two trials had been done with the  
5 single symptom VAS, and we were worried that by  
6 switching the endpoint for the confirmatory trial  
7 that we might have trouble comparing the third  
8 trial to the first two trials that had been  
9 submitted. And that's why the primary symptom VAS  
10 was included as a key secondary endpoint so that we  
11 could try to make those cross-trial comparisons.

12 DR. PLATTS-MILLS: Just remind me, what is  
13 the term -- you described a letter that had some  
14 term at the top of it, I think.

15 DR. LIMB: Right. I think that's referring  
16 to the SPA no agreement letter, and that's  
17 basically saying that we were not at a point or  
18 not -- we felt we were not in a position to enter a  
19 binding agreement regarding the FAST-3 protocol.  
20 However, in the conversations that we had around  
21 the time that letter was issued, we conveyed that  
22 the general design of FAST-3 and the endpoints that

1 had been designated were acceptable.

2 DR. PLATTS-MILLS: Thank you.

3 DR. KRISHNAN: Dr. Mauger, I think you had a  
4 question.

5 DR. MAUGER: Thank you. This is sort of a  
6 follow-up to a question that I posed earlier. I'm  
7 trying to understand the interpretation of VAS and  
8 to estimate the magnitude of the treatment effect.  
9 When I look at the Kaplan-Meier curves, I see the  
10 flat line in both groups between 8 and 18 hours,  
11 which I'm thinking represents the fact that there  
12 were no measurements taken in that time. And I'm  
13 concerned about the possibility of artifact in the  
14 median estimates. The confidence intervals are  
15 much wider for the placebo group confidence  
16 interval estimate than for the icatibant.

17 So the question, I guess, in terms of  
18 measuring the magnitude of the effect, do you feel  
19 that median time to effect is the appropriate way  
20 to talk about magnitude of effect?

21 DR. LIMB: So I think that's an important  
22 point that might merit further discussion this

1 afternoon. And certainly, with small sample sizes,  
2 we had some concerns about picking a median-based  
3 endpoint. And then looking across the studies,  
4 we've seen that the comparators behave very  
5 differently across the three trials so that was an  
6 additional issue. And, really, that touches upon  
7 the wide confidence interval that you've observed  
8 for the placebo in one study.

9 But I think the data are what they are, and  
10 so we're going to turn around and ask you-all to  
11 decide whether you feel that that was an  
12 appropriate endpoint and whether you can interpret  
13 that in a clinically meaningful way.

14 DR. KRISHNAN: So if I could follow up to  
15 Dr. Mauger's question related to this, so when you  
16 see a flat line, there are no new events happening.  
17 So one way that could be happening is that no  
18 information has been gathered, therefore, no  
19 events, or the information's being gathered, but  
20 there are no new events. And either of those would  
21 give you a flat line.

22 So what I wanted to ask is, was there

1 information being gathered during the latter phases  
2 of the observation period, or if you don't know,  
3 perhaps we can also ask the sponsor related to  
4 this.

5 Dr. Limb, what are your thoughts on that?

6 DR. LIMB: So I don't recall the details of  
7 the assessments that were done in the later period.  
8 I know that the most intensive assessments were  
9 done within the first 12-hour period. So I'll ask  
10 the sponsor. Maybe they can fill us in.

11 DR. CAMMARATA: Yes, the assessments were  
12 done multiple times within the first 48 hours.  
13 That was the most frequent time that assessments  
14 were done, but then assessments continue to be done  
15 up through five days. And those were done -- we  
16 can't keep the patients in a clinic for five days,  
17 so they continued those at home, and they did those  
18 assessments three times a day in the latter days of  
19 the study.

20 DR. KRISHNAN: So if I could -- just to  
21 clarify, in my mind, the participants were asked  
22 about their symptoms three times a day, and if they

1 did not provide data, were they essentially  
2 censored or were they included in there? How did  
3 you deal with the fact that people may not answer a  
4 question three times a day?

5 DR. CAMMARATA: Can I ask Dr. Amato to  
6 comment about missing data?

7 DR. AMATO: Yes, I'm David Amato, senior  
8 director of biometrics at Shire HGT. Overall,  
9 there was actually very little missing data. If  
10 you look at the totality of assessment and time  
11 points that were required by the protocol, there  
12 were only about 2.6 percent that were actually  
13 missing for the primary assessment, the primary  
14 symptom VAS. And if you look at whether any single  
15 component of the composite VAS was missing, it was  
16 about 6.3 percent, so very little missing data  
17 overall.

18 The way we dealt with it in the analysis is  
19 that you had to have three consecutive non-missing  
20 measurements to define the response, the time to  
21 onset of response. So if during that period where  
22 you're looking for the confirmation, there was a

1 missing observation, then that time point was just  
2 ignored and we went to the next time point. So if  
3 there were three measurements out of four with one  
4 missing, you still could define onset of response.

5 DR. KRISHNAN: So, in summary, very little  
6 missing data?

7 DR. AMATO: Very little missing data  
8 overall.

9 DR. KRISHNAN: Okay. So flat lines  
10 represent no new events, not missing bits of  
11 information?

12 DR. AMATO: Right.

13 DR. KRISHNAN: Okay.

14 Dr. Mauger, I don't know if that's where you  
15 were heading with that, but is there anything else  
16 you wanted to ask related to that before we go on  
17 to other questions?

18 DR. MAUGER: Well, yes, a follow-up then.  
19 You had mentioned before the possibility of someone  
20 having been treated at 9:00 p.m. and therefore, the  
21 12-hour windows would occur being relevant to when  
22 they could make it to the office. So if someone

1 was treated at 9:00 p.m., does that mean that they  
2 were woken up every hour in the middle of the night  
3 for these four-, five-, six-, seven-, eight-hour  
4 assessments to ask how they felt?

5 DR. RIEDL: (Shakes head yes.)

6 DR. MAUGER: Right, I know they were  
7 hospitalized. So they were woken up every hour to  
8 ask them how they felt.

9 DR. KRISHNAN: Okay. Let me go back to this  
10 list here. Let me just say the order so the  
11 committee members know where we're heading.

12 Mr. Mullins, Dr. Greenberger, Dr. Platts-Mills,  
13 those are the list of folks we have for the current  
14 session. And we're actually running perhaps a  
15 little ahead. Let's see. And if so, we might go  
16 back to the opportunity to ask questions of the  
17 sponsor, but let's see how it goes.

18 So Mr. Mullins.

19 MR. MULLINS: I looked at the data, and I  
20 want to understand if their data had additional  
21 information on neurological analysis of the usage  
22 of icatibant because, obviously, most of the data

1 looks at intermittent use. So based on a  
2 longitudinal review of the usage of this therapy,  
3 did you see any -- have any indication, or is there  
4 any data on the addictive properties, response  
5 receptors to this particular therapy?

6 DR. LIMB: So we didn't identify any  
7 information to make us concerned about potential  
8 addiction or tolerance.

9 I'll ask if the sponsor has any additional  
10 information to address your question.

11 DR. CAMMARATA: No. Based on the mechanism  
12 and the effect of icatibant, that's not expected  
13 and it's not seen.

14 MR. MULLINS: But what was the length of  
15 your study? How long did you -- what was the  
16 follow-up done after the --

17 DR. CAMMARATA: Sure. The patients in the  
18 trial the longest, our trial has been up to  
19 36 months, three years, for patients in the open  
20 label extension trial. And patients with HAE are  
21 treated intermittently for their attacks. And, as  
22 I said, the longest has been up to 36 months.

1 MR. MULLINS: Okay.

2 DR. KRISHNAN: Next on our list is  
3 Dr. Greenberger.

4 DR. GREENBERGER: I have two questions. The  
5 first is on use of composite scores.

6 Did the agency also have questions about  
7 using composite scores for the two other products  
8 that have been approved for acute use since  
9 composites were used in those studies?

10 DR. LIMB: So I think it's probably best for  
11 us to keep our conversation directed more to this  
12 particular product. I think the issue of composite  
13 scores, when we talked about it in the context of  
14 icatibant, we felt that obtaining composite  
15 information might give us a more full picture of  
16 what was happening in a HAE attack because it was  
17 clear to us from looking at the data with the  
18 original two trials that patients were coming in  
19 with more than one symptom. And so it's a complex  
20 disease presentation, and a single symptom VAS, we  
21 felt might not have been adequate to really capture  
22 what was happening with the patient.

1           We did have concerns, though, about  
2           switching the endpoint from the first two studies  
3           to the third. So I think there was some question  
4           on our part about introducing a composite endpoint  
5           in the FAST-3, but the overall feeling was that  
6           composite endpoints could potentially give us more  
7           information on what is a very complicated disease  
8           to study.

9           DR. GREENBERGER: And the other question is  
10          on the use of data for rescue meds. Do you have  
11          information on -- the marker would be use of  
12          narcotic medications in the first four hours for  
13          placebo versus actively treated patients.

14          DR. LIMB: So I believe that in FAST-1 and  
15          FAST-3, the most commonly used rescue medication  
16          were opioids. In FAST-2 -- actually, I'm sorry. I  
17          might have that reversed. No, no, FAST-2. I  
18          believe that C1 inhibitor product was actually the  
19          most commonly used rescue product. But I don't  
20          have the exact numbers in my head, so I can ask the  
21          company to give us those, that breakdown.

22          DR. KRISHNAN: Does the sponsor have a

1 response?

2 DR. CAMMARATA: Slide up, please. This is  
3 the patients that used rescue med, and this, I  
4 believe, is at any time during the trial. This is  
5 any time, so it could be out five days where they  
6 used -- and meds could be a variety of medications,  
7 including ibuprofen, diclofenate, and opioids. So  
8 these are the meds that were used for the worsening  
9 of -- or recurrence -- if patients had any  
10 worsening of their symptoms. So you can see a  
11 variety: diphenhydramine, opioids, steroids.  
12 There are a variety of ways to look at that  
13 overall, and, as I said, this one is showing the  
14 worse -- when patients had any kinds of complaints  
15 of symptom changes specifically.

16 DR. KRISHNAN: Great. Thank you.

17 I think Dr. Platts-Mills.

18 DR. PLATTS-MILLS: There's been several  
19 questions about this evaluation of the late  
20 response at 24 and 48 hours, at which time symptoms  
21 are clearly on average dramatically reduced. And I  
22 think that thinking about the disease, what

1 patients -- I'd just like to make the comment that  
2 what patients are scared about is whether this is  
3 going to proceed, whether the pain is going to  
4 continue, whether it's going to proceed. And it's  
5 the initial improvement that actually is what they  
6 want and that's the relief, the moment that they  
7 know this is not progressing.

8 In terms of time, I can remember telling  
9 people that because of hearing descriptions in the  
10 emergency room, if you go into the emergency room  
11 and you feel that your tongue is swelling and a  
12 doctor looks at you and says your tongue is fine,  
13 you sit in the waiting room for two or three hours  
14 to make sure that it isn't swelling because the  
15 doctor doesn't know, and that they will sit there  
16 for hours, very afraid that it's going to progress  
17 and not knowing. And, therefore, the initial move  
18 that something is improving may be exactly what the  
19 patient needs.

20 DR. KRISHNAN: Thank you.

21 I think, Dr. Tracy, you had a question.

22 DR. TRACY: Just a clarification. Getting

1 back to the pharmacology and toxicology and the  
2 reproductive component, you mentioned that -- well,  
3 obviously, these are in animal studies. Delayed  
4 parturition was observed, dose dependent effect on  
5 reproductive organs, specifically testicular and  
6 uterine atrophy in animals. I was just wondering  
7 if you had any long-term concerns for us, with  
8 people.

9 DR. LIMB: So I guess two things to consider  
10 are: what information is available to us now, and  
11 then, two, what is the anticipated use of the  
12 product. As far as the information that's  
13 available to us now, it is fairly limited. We have  
14 some experience with women who became pregnant  
15 during the clinical trials, and you heard the  
16 outcomes of those pregnancies earlier today. But  
17 for the most part, patients were supposed to be on  
18 contraception, and the studies really weren't  
19 designed to look at the effects of icanitabant on  
20 fertility or reproduction. So it's hard to go  
21 beyond what information we have right there.

22 There is an ongoing study to look at the

1 effect of icatibant on different reproductive  
2 hormone levels, and perhaps that study when it's  
3 complete will give us some additional insight into  
4 this possible risk.

5 As far as how we anticipate the drug to be  
6 used, I think it does vary from individual to  
7 individual. There are patients who've enrolled  
8 into the open label extension who haven't really  
9 required any additional treatment or maybe one  
10 treatment in a year-long period. And so it's hard  
11 to imagine that that kind of sporadic exposure  
12 would have any lasting toxicity on the reproductive  
13 cycle or reproductive organs. But, certainly,  
14 there are individuals who have required more  
15 frequent treatment due to the severity of their  
16 disease. And I think that's a consideration as we  
17 think about whether or not we have sufficient  
18 safety information for the product.

19 DR. TRACY: I guess as I sit here, I'm  
20 thinking about my patients, and I've got -- almost  
21 all of them, male and female, are of childbearing  
22 age. And I have to think about how I would counsel

1       them as you go through risk benefits. And I don't  
2       have an answer, either. I'm just kind of thinking  
3       about how I'm going to address that question should  
4       it come up, and it will come up.

5               DR. KRISHNAN: Are there additional  
6       questions from the committee members to the FDA for  
7       clarification?

8               [No response.]

9               DR. KRISHNAN: Okay. So we have about five  
10       minutes before we're supposed to break for lunch.  
11       I would like to suggest, if it's acceptable to the  
12       committee members, that we have a list of about  
13       four committee members wanting to ask the sponsor  
14       for some clarification that we had to stop that  
15       discussion on. There is an opportunity, I guess,  
16       to maybe ask one question or two, depending on how  
17       it goes.

18               Is that acceptable or do folks want to take  
19       a break for lunch at this point? Should we go  
20       ahead and proceed with questions?

21               [No verbal response.]

22               DR. KRISHNAN: So I'm hearing mostly nods;

1 I'm seeing mostly nods, I should say. So I will  
2 proceed.

3 Dr. Posner, you were actually on the list of  
4 the first questions to the sponsor for  
5 clarification. Go ahead.

6 DR. POSNER: Most of the questions I had  
7 were already asked about the kit, but I did have an  
8 additional question. Looking at the picture of the  
9 syringe, I couldn't tell whether you had a luer  
10 lock on the syringe and what the size of the needle  
11 was that was being used, because that's important  
12 to people that are taking injections.

13 DR. CAMMARATA: I'm smiling because I'm  
14 going to ask Jim Weston. Could you talk about the  
15 needle? We talked about that yesterday.

16 DR. WESTON: Sure. Jim Weston, senior  
17 director of regulatory affairs at Shire.

18 The needle is a 25-gauge, 16-millimeter  
19 length needle, typically used for subcutaneous  
20 injections.

21 DR. POSNER: But is the syringe a luer lock  
22 or is it just a --

1 DR. WESTON: It has a luer lock on it,  
2 correct.

3 DR. POSNER: Great. And is there ethanol in  
4 the packet?

5 DR. WESTON: I'm sorry?

6 DR. CAMMARATA: Pads, site preparation.

7 DR. POSNER: Ethanol for site preparation,  
8 ethanol swabs.

9 DR. WESTON: Not in the package itself, but  
10 it typically would be part at the time -- provided  
11 as part of the training materials.

12 DR. POSNER: I had one other question about  
13 the injection site since the injection site is  
14 being suggested as sub-Q abdominal. And since the  
15 number of symptoms are abdominal, if you're  
16 injecting into an area that's already swollen and  
17 filled with intracellular fluid, extracellular  
18 fluid, are you having a delay in response to the  
19 medication by dilution versus going to a different  
20 injection site?

21 DR. CAMMARATA: We do recommend that  
22 patients go away from the injection site. We

1 haven't seen a change in the effect of that. I  
2 think I'd ask Dr. Maurer if he can comment because  
3 you're actually dosing, have been dosing patients  
4 for the last two or three years.

5 DR. MAURER: Sure. Marcus Maurer from  
6 Berlin. So there's actually two issues here. If  
7 you have an abdominal attack, it's not necessarily  
8 the skin, but it's really your abdomen. So you  
9 still have that little extra where you can inject,  
10 and it really doesn't matter.

11 The other thing is that we've had reports  
12 now from many, many patients that have injected  
13 multiple times, and we've learned quite a bit from  
14 it. And just maybe to bring perspective to that  
15 whole injection site reaction, that is dependent a  
16 lot on how you inject. And the patients actually  
17 do it much better than our young residents do it  
18 that are in the ER getting nervous when the patient  
19 comes in.

20 There's actually four points. So the  
21 patient almost never injected cold. When we take  
22 it, we take it out of the fridge. The patients

1 know that -- at least some patients know when it's  
2 cold, it hurts. The second thing is they don't do  
3 that doctor thing. They don't squirt it out. So  
4 they want all of it, and thereby there's no little  
5 residue on the tip of the needle. So you're not  
6 skin prick testing with icatibant. You're bringing  
7 the needle in, and the little air that you inject  
8 with it really doesn't matter.

9 Point 3 and 4 are really they take a lot  
10 longer than we take, so they take minutes, up to  
11 five minutes, to inject these 3 mils, so it's much  
12 more comfortable for them. And they inject nice  
13 and deep, and by "nice and deep," I mean they go in  
14 a 90-degree angle. They make sure it's in the  
15 sub-Q, and it's not intradermally where you have  
16 muscle cells and nerves and you get that site  
17 reaction.

18 So that's what we learned from our patients,  
19 and we pass it on to other patients. And many  
20 patients that inject that way do not have any site  
21 reactions at all. So just to put it into  
22 perspective, it's really not a big problem.

1 DR. KRISHNAN: Okay. I think we're at  
2 12:00 noon, so I think we're going to take a lunch  
3 break. Let me just make a couple of comments.  
4 We'll take an hour lunch break. We'll reconvene  
5 again in this ballroom in 60 minutes at essentially  
6 1:00 p.m. Panel members are reminded that please  
7 remember that there should be no discussions of the  
8 issue at hand during lunch amongst yourself or with  
9 any member of the audience. Thank you very much.  
10 See you at 1:00.

11 (Whereupon, at 11:59 a.m., a luncheon recess  
12 was taken.)  
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1                   A F T E R N O O N     S E S S I O N

2                                   (1:00 p.m.)

3                                   **Open Public Hearing**

4                   DR. KRISHNAN:   So we're going go ahead and  
5                   get started for the afternoon session.   Again,  
6                   please take your seats, and thank you for joining  
7                   us for this meeting.

8                               Both the Food and Drug Administration and  
9                   the public believe in a transparent process for  
10                  information gathering and decision making.   To  
11                  ensure such transparency at the public hearing  
12                  session of the advisory committee meeting, FDA  
13                  believes it is important to understand the context  
14                  of an individual's presentation.

15                               For this reason, FDA encourages you, the  
16                  open public hearing speaker, at the beginning of  
17                  your written or oral statement to advise the  
18                  committee of any financial relationship that you  
19                  may have with the sponsor, its product, and if  
20                  known, its direct competitors.

21                               For example, this financial information may  
22                  include the sponsor's payment of your travel,

1 lodging or other expenses in connection with your  
2 attendance at the meeting. Likewise, the FDA  
3 encourages you at the beginning of your statement  
4 to advise the committee if you do not have any such  
5 financial relationship. If you choose not to  
6 address this issue of financial relationships at  
7 the beginning of your statement, it will not  
8 preclude you from speaking.

9 The FDA and this committee place great  
10 importance in the open public hearing process. The  
11 insights and comments provided can help the agency  
12 and this committee in their consideration of the  
13 issues before them. That said, in many instances  
14 and for many topics here, there will be a variety  
15 of opinions. One of our goals today for this  
16 public hearing is that it be conducted in a fair  
17 and open way where every participant is listened to  
18 carefully and treated with dignity, courtesy and  
19 respect. Therefore, please speak only when  
20 recognized by the chair. Thank you for your  
21 cooperation.

22 So we'll begin with the first open public

1 hearing comment by Dr. Marcus Maurer.

2 DR. MAURER: Thank you very much. Again, my  
3 name is Marcus Maurer. I'm a professor of  
4 dermatology at the University Hospital of Charite  
5 Berlin with a large angioedema clinic, more than  
6 100 patients with hereditary angioedema, and I'm  
7 here on their behalf.

8 As stated, I am an investigator, have been  
9 an investigator for studies on icatibant but also  
10 for Cinryze. I'm also an advisor for ViroPharma  
11 and Behring and Shire.

12 But this is not about me. This is about our  
13 patients who have received icatibant over the  
14 last -- up to three years. About 60 of our  
15 patients are on self-medication. Many of them have  
16 used this treatment for many years and for a long  
17 time, and they have asked me to report on this.  
18 And I actually provided letters to all of you who  
19 are in front. I can only read parts of them, which  
20 I will do, but I encourage you to read the entire  
21 letters, and I will focus on some of the  
22 statements.

1           The first one is by Hannah Ziegland (ph).

2           It's also the longest one. But here it goes.

3           So she writes, "Dear Doctor, for a good  
4           three years, I am your HAE patient. During that  
5           time, my life has changed very much even though I  
6           have already suffered from HAE for a number of  
7           decades. First, the diagnosis of HAE and the  
8           following therapy changed my life in a positive  
9           way. Especially the medication Firazyr, it changed  
10          the quality of my life enormously.

11          "Even though I've had this illness since I  
12          was young, I now feel much better with HAE in my  
13          personal and work life. The opportunity for self-  
14          injection of Firazyr has contributed a lot. It  
15          enables me to react to the HAE-induced attacks  
16          without having to miss work. Before, I had to go  
17          call the ambulance or go to the emergency room,  
18          which made me miss work very often.

19          "My personal life, my social contacts and  
20          making plans and having them come true, all that  
21          has become easier with the possibility of self-  
22          injection and, not to forget, my self-confidence

1 and psychological stability improved. For example,  
2 I can go on a trip and choose the type of  
3 transportation, a normality which would not be  
4 possible without the syringe in my luggage. Before  
5 that time, I had to cut back my recreational  
6 activities and/or my social contacts. I lost trust  
7 in my employment," which means is that she was  
8 afraid she was going to her lose her job.

9 "Today, the self-injections give me the  
10 security for my daily living and the sureness that  
11 I need not imagine my illness. Besides the slight  
12 redness, the self-injection for treating my HAE  
13 attacks, I don't have any side effects. My  
14 experience of Firazyr self-injection is all-around  
15 positive. I would like to take this opportunity to  
16 thank you."

17 These are just translations from the  
18 original letters. I haven't added anything to it,  
19 but I will be happy to comment on them, should you  
20 want me to.

21 The second one is from Gabriella Hahn (ph),  
22 and I picked a quote that actually reflects on the

1 difference between self-injection and a physician  
2 injection. And she writes, "After you have given  
3 me a prescription of Firazyr, I tested the  
4 medication during an abdominal attack, and after  
5 15 minutes, the pain was reduced. I was really  
6 happy about that. The only problem was the ER  
7 where they gave me the injection. I had to endure  
8 the severe pain because of a long waiting time.

9 "I'm sure you can imagine how nice it was to  
10 get the okay to do the injections by myself. The  
11 frequency and severeness of the attacks did not  
12 change, but I do not have to endure the pain for  
13 long and quickly feel better. I have to live with  
14 this illness, but now it's much easier to live with  
15 it."

16 Then I brought a letter from a 20-year-old  
17 patient. And I should say that most of these  
18 letters are volunteered, and we have a lot more of  
19 reports of our patients over the last three years  
20 that just feel the need to tell us how this has  
21 changed their lives. They write e-mails, they call  
22 us, or they report on this when we see them in our

1 regular checkup visits.

2           Now, this is from Rebecca. Rebecca  
3 Tutez (ph) is 20 years old, and she writes, "After  
4 being insecure in the beginning, I'm now managing  
5 to inject subcutaneously with the medication. It  
6 is important to give the injection when the syringe  
7 is warm," in parentheses, "room temperature. As  
8 soon as the temperature is too cold, I have a  
9 discomfort during the injection, slight to strong  
10 pulling sensation. Within a short time after the  
11 treatment, I'm without any pain. I can continue my  
12 education" -- she's a student at the  
13 university -- "without missing classes and I can  
14 better plan, for example, vacation, going out.  
15 Firazyr gives me great relief."

16           Now, this shows that even teenagers -- she  
17 was a teenager when she first learned how to do the  
18 injection. She was really sort of skeptic about  
19 being able to do it, know and learn how to do it,  
20 and in time feel comfortable with that treatment.

21           This is from Katrine Lipsky (ph), and it  
22 actually shows that it's not just the where but

1 also the when patients can treat, that they do  
2 treat early on. They recognize their attacks. She  
3 writes, "Now something revolutionary happened to  
4 me. Thanks to you, a new medication called Firazyr  
5 has recently come to the market" -- I'm not taking  
6 all the credit but -- "which allows me to lead an  
7 independent life.

8 "I now carry the syringe with me all the  
9 time, and I'm able to inject myself in good time  
10 during even the slightest swelling attack.  
11 Therefore, the pain doesn't get that bad, and the  
12 attack is stopped in due time by me without having  
13 to search for a doctor. Since Firazyr, my quality  
14 of life has improved." And another way to  
15 translate -- these are all written in German and  
16 translated by one of my American study nurses.  
17 Another way to translate it, "Since Firazyr, I  
18 actually have quality of life."

19 The last one is very short. This is from  
20 the patient who taught us that it is much better to  
21 inject slowly. And he says -- a 59-year-old  
22 patient, two kids, three grandchildren, has had it

1 for a long time. He writes, "Thanks to Firazyr and  
2 the possibility to give myself the injections, I  
3 have an absolutely new and good attitude towards  
4 life again. And I would like to encourage every  
5 patient who suffers from the same rare illness to  
6 treat themselves with this medication."

7           These are only spotlights of what our  
8 patients tell us, but if you put it all together,  
9 it shows that the patients are very thankful for  
10 having this treatment option. This is what they've  
11 been looking for, for a long time, not to have to  
12 react and be helpless and depend on others, but to  
13 take control of their lives, to know -- they have  
14 confidence that anywhere, anytime, they can control  
15 their disease. They start to travel. They start  
16 to take real options that they weren't able to take  
17 before. They come back to us, and they have  
18 changed. Their lives have changed, and I think  
19 these letters reflect this.

20           So on behalf of my patients, this is an  
21 overall very satisfying experience, not just for  
22 them, also for us. It is not easy and a lot of

1 responsibility to treat patients with hereditary  
2 angioedema. It takes a lot of effort, but a lot of  
3 getting to know your patient, and getting to know  
4 their families, and getting to know their plans and  
5 their vision. And this is actually a great tool  
6 for us to give to our patients to take more control  
7 of their own lives. So thank you for allowing me  
8 to bring these testimonials of my patients.

9 DR. KRISHNAN: Thank you, Dr. Maurer.

10 Our next individual is Ms. Lanet Long. I'm  
11 sorry. Ms. Janet Long. I'm sorry about  
12 mispronouncing your name.

13 MS. LONG: That's quite all right.

14 Good afternoon. My name is Janet Long, and  
15 I'm the executive vice president of the United  
16 States Hereditary Angioedema Association. I do not  
17 have any financial ties to Shire. I am not a  
18 shareholder, and the HAE Association paid for my  
19 travel here today. I thank you for providing HAE  
20 patients with an opportunity to speak about the  
21 critical need for a safe and effective nonsteroidal  
22 HAE therapy.

1           This morning I wear two hats. I stand  
2 before you as a patient who has suffered with HAE  
3 and whose own search for an accurate diagnosis took  
4 40 years, but I also stand before you to represent  
5 a small but empowered rare disease group, the HAE  
6 Association. And it is with my HAE hat that I  
7 would like to provide you with an overall  
8 understanding of where HAE treatment stands today.

9           Perhaps the best characterization of how HAE  
10 affects patients appeared in a 1996 New England  
11 Journal of Medicine article. "Patients with a  
12 deficiency of C1 inhibitor are not just an  
13 interesting model for study. They are critically  
14 ill, and many have ancestors who died suddenly from  
15 suffocation. Patients live in constant dread of  
16 life-threatening laryngeal obstruction."

17           Ladies and gentlemen, hereditary angioedema  
18 still represents a catastrophic unmet medical need  
19 in the United States. Many HAE patients continue  
20 to experience acute abdominal and laryngeal attacks  
21 notwithstanding ongoing therapy. In 2010, our  
22 association received word of 10 HAE-related deaths.

1 It is our fervent hope to not have one HAE death in  
2 2011.

3 In this regard, we are delighted that the  
4 committee will be considering the Shire product  
5 today. An effective acute therapy will serve to  
6 finally ameliorate HAE's dreadful morbidity.  
7 Prophylaxis can only address a portion of the  
8 problem faced by HAE patients today. There is no  
9 doubt that HAE is a very unpredictable disease. As  
10 noted earlier, the scientific literature provides  
11 ample evidence that patients can have breakthrough  
12 life-threatening laryngeal or excruciating  
13 abdominal attacks no matter what therapy they are  
14 using.

15 In a similar vein, we must ask ourselves why  
16 an HAE patient who only has one attack a month or  
17 less should be relegated to the use of anabolic  
18 steroids for prophylaxis when less severely  
19 affected patients could manage their HAE by working  
20 with their physicians to set up on-demand access  
21 for acute attacks.

22 We have seen the damage that side effects of

1 androgen use can cause to the overall health of HAE  
2 patients. Every new therapy brings greater choice  
3 in the patient's individual HAE treatment plan.  
4 You have before you today an abundance of clinical  
5 information that provides statistically significant  
6 evidence of the effectiveness of Firazyr as a  
7 treatment for hereditary angioedema.

8 We hope that the committee recognizes that  
9 everyone in our beleaguered patient community  
10 deserves the opportunity for access to a  
11 nonsteroidal alternative HAE therapy that provides  
12 on-demand treatment for this still dangerous,  
13 unpredictable and potentially fatal disease. The  
14 evidence is compelling, the need is overwhelming  
15 and any further delay in helping this underserved  
16 patient community, as you will hear from some of  
17 our patients speaking today, would be tragic.

18 This week I received a letter from  
19 Hereditary Angioedema International, HAEI, and I  
20 would like to provide just a quick, couple excerpts  
21 from that letter for you.

22 "HAEI is a nonprofit global umbrella patient

1 organization dedicated to raising awareness of  
2 C1 inhibitor deficiency around the world. It asks  
3 that we remember that HAE has been reported, that  
4 laryngeal attacks can fully close an airway in just  
5 20 minutes. From a patient's perspective then,  
6 every attack should be considered a potentially  
7 life-threatening attack.

8 "The EMA registered icatibant as an orphan  
9 drug in 2008. In March of this year, the label was  
10 upgraded to include self-administration. We, HAEI,  
11 believe that icatibant is an important new therapy  
12 that could be of significant benefit to HAE  
13 patients in the United States. Convinced that  
14 Firazyr is a potentially lifesaving medicine, we  
15 urge the FDA to license icatibant as a self-  
16 administered acute attack HAE therapy." Signed  
17 Henrik Boysen, executive director, HAEI.

18 The HAE Association in the U.S. agrees, and  
19 we thank you very much for the privilege of  
20 addressing you today.

21 DR. KRISHNAN: I think we're going to have  
22 Ms. Jenny Barnes next.

1 MS. BARNES: Hello, my name is Jenny Barnes,  
2 and I live in North Carolina. I do not have any  
3 financial ties to Shire. I am not a shareholder,  
4 and the HAE Association paid for my travel here  
5 today.

6 I am appearing before you today as the  
7 mother of a young man severely affected by HAE. My  
8 son Jim began suffering from severe abdominal HAE  
9 attacks at the age of five, and I can vividly  
10 recall the horror of having to watch my child  
11 suffer until the only medicine we had at our  
12 disposal, the painkiller Demerol, would mercifully  
13 put him to sleep.

14 In the subsequent years, Jim bravely endured  
15 frequent disabling episodes of swelling and pain.  
16 The relentless onslaught of HAE attacks resulted in  
17 an inordinate number of missed schooldays and  
18 prevented him from the day-to-day activities  
19 enjoyed by boys his age. As if the pain and  
20 disability of his abdominal attacks weren't enough,  
21 Jim had his first throat swelling attack at the age  
22 of 12. This dangerous life-threatening event

1 required intubation and an ICU stay that lasted  
2 three long and frightening days.

3           This episode of throat swelling provided  
4 tangible evidence that Jim's HAE was worsening, and  
5 at that point we as parents had no choice other  
6 than to start him on an anabolic steroid. While  
7 these medicines are contraindicated in 12-year-old  
8 boys, we concluded that the risk from death from  
9 suffocation outweighed the dangers associated with  
10 the androgen therapy in a preteen youngster.

11           The years of emotional trauma brought on by  
12 pain, the ever looming threat of death by  
13 suffocation, and the side effects of anabolic  
14 steroid therapy took their toll on Jim. When he  
15 was 15, he suffered an emotional meltdown that was  
16 clearly steroid-related. The steroid rage that Jim  
17 exhibited landed him in a protective custody  
18 setting.

19           In the last two years, Jim began to show a  
20 glimmer of promise thanks to intensive therapy and  
21 the fact that his maturation diminished the  
22 steroids' side effects. By age 19, he had a job,

1 and we finally began to see the makings of a young  
2 man who was proving to be an asset to society.

3 Ladies and gentlemen, I will never know what  
4 kind of adult my beloved Jim would have become  
5 because on June the 6th, 2008, Jim was admitted to  
6 the emergency room with laryngeal swelling, and an  
7 hour or so later, died from what an autopsy noted  
8 as suffocation due to laryngeal edema.

9 I am here addressing you today because Jim's  
10 death and the deaths of at least 10 other HAE  
11 patients who died from laryngeal attacks or  
12 complications following a laryngeal attack over the  
13 past 18 months were totally preventable. I stand  
14 before you heartbroken but resolute in my desire to  
15 do whatever I can to prevent another mother from  
16 the unspeakable grief that accompanies losing a  
17 child to HAE. I will never have the privilege of  
18 celebrating any of my son's achievements, helping  
19 him through life's inevitable bumps or experiencing  
20 the joys of attending his wedding, holding my  
21 grandchildren and sharing in all of life's  
22 milestones.

1           You have the power today to recommend  
2 approval of a lifesaving medicine. Please make  
3 sure that no other HAE mother has to cope with the  
4 tragic, heartbreaking yet totally preventable death  
5 of a precious child. Thank you.

6           DR. KRISHNAN: Thank you.

7           Ms. Michelle Williamson.

8           MS. WILLIAMSON: Good afternoon. My name is  
9 Michelle Williamson, and I am from Texas. I do not  
10 have any financial ties to Shire. I'm not a  
11 shareholder, and the HAE Association paid for my  
12 travel here today.

13           I'm one of thousands of HAE patients who  
14 have suffered from this debilitating and life-  
15 threatening rare disease. During 23 long years of  
16 anabolic steroid therapy, I suffered through  
17 countless emergency room visits for attacks that  
18 steroids did not prevent and that not only involved  
19 excruciating abdominal pain but also involved my  
20 airway. These attacks forced me to endure more  
21 than a dozen laryngeal intubations and emergency  
22 tracheotomy. I was disabled for the majority of my

1 adult life.

2 I'm a living, breathing example of why HAE  
3 patients in the United States need better treatment  
4 alternatives but not only for preventing HAE  
5 attacks. Lifesaving acute therapy is every bit, if  
6 not more, important, and I truly hope the committee  
7 understands that throat attacks and excruciating  
8 abdominal attacks can occur at any time even for  
9 patients who are on prophylaxis. A tragedy that  
10 almost took my life illustrates just this point.

11 After receiving nonsteroid preventative  
12 treatment for a number of months, I felt joy I  
13 cannot describe to you, joy for the first time in  
14 well over a dozen years. I decided I was now well  
15 enough to take a weekend trip. I had what can only  
16 be described as an idyllic getaway until HAE  
17 cruelly attacked.

18 While on the way to catch my flight home, I  
19 realized I was experiencing a laryngeal attack, and  
20 it was coming on fast. My travel companion noticed  
21 that I was having trouble swallowing. We were  
22 lucky enough to flag down a passing police officer

1 who called an ambulance for me. Once at the ER,  
2 despite my objections, the doctors treated me with  
3 medications HAE patients know don't work,  
4 epinephrine, antihistamines. They also tried fresh  
5 frozen plasma to no avail.

6 The quick advance of the swelling in my  
7 throat and the baffled look on the faces of the ER  
8 staff made me fear for my life. Again, I prepared  
9 myself to die. I told my friend to tell my young  
10 son that I loved him, that I was very proud of him,  
11 and that I was sorry. As I laid there helpless,  
12 sensing my airway tightening, I remember coughing  
13 and nothing else.

14 I spent the next seven days intubated and  
15 sedated. My lungs had collapsed. I'd lost the use  
16 of my leg muscles from being immobilized for so  
17 many days. I could barely manage to sit up until  
18 day 11 when I took just three steps,  
19 hyperventilated and fainted. I woke up hearing the  
20 hospital doctors trying to decide whether or not to  
21 intubate again and telling me I should consider a  
22 permanent tracheotomy. After 19 days in the

1 hospital, an 80,000-dollar bill, I was sent home  
2 with antibiotics to treat hospital-acquired  
3 pneumonia and endured weeks of physical therapy  
4 learning to use my legs so I could walk again.

5 The tragedy, ladies and gentlemen, is that  
6 this entire situation could have been avoided by  
7 the quick administration of a medication  
8 specifically for the treatment of acute HAE  
9 attacks. As you deliberate approving the Shire  
10 product today, I kindly ask you to consider  
11 patients like me who desperately need this therapy  
12 for treating dangerous acute HAE attacks, who  
13 desperately hope to avoid the very situation you  
14 have so kindly listened to me describe. Thank you.

15 DR. KRISHNAN: Thank you.

16 Ms. Amanda Dillon.

17 MS. DILLON: Good afternoon, my name is  
18 Amanda Dillon, and I'm from Florida. I also very  
19 much appreciate the opportunity to address this  
20 committee. I do not have any financial ties to  
21 Shire. I am not a shareholder, and the HAE  
22 Association paid for my travel here today.

1           I am going to take a slightly different  
2 approach during my time with you this afternoon.  
3 Let me ask each one of you to step out of your role  
4 as medical professionals for the next couple of  
5 minutes and think of me as your wife or your sister  
6 or your daughter. Please spend just a few moments  
7 of my life as a severely-affected HAE patient.

8           Imagine waking up one morning and as you get  
9 out of bed, you realize your feet are so swollen  
10 that even a short walk to the shower is going to be  
11 very painful. When you stand up, your feet feel  
12 like they are ready to explode from trying to  
13 support your body weight. But soon you come to the  
14 conclusion that you have no choice to get moving to  
15 that bathroom because the sharp gnawing pain in  
16 your stomach signals a sickening and urgent need to  
17 throw up.

18           The fluids that have caused your swelling  
19 have leaked out of your circulatory system and your  
20 blood pressure is very low. The lightheaded faint  
21 feeling you are experiencing makes you wonder if  
22 you will even make it to the bathroom before

1 passing out. You want to ignore the dangers of not  
2 seeking medical help for what you know is going to  
3 be a miserable HAE attack. Who will understand  
4 these rarely seen symptoms? You want to just stay  
5 home and tough it out, but then the next wave of  
6 excruciating pain hits. And your spouse or parent  
7 intervenes and convinces you to make yet one more  
8 trip to the ER.

9 By now, you are so weak you can barely  
10 muster the emotional strength to call it sick at  
11 work, but you have to. And when you do, you can  
12 hear your boss' frustration in his voice because  
13 this is the second time you've called out sick in  
14 the past week and a half. The stress only adds to  
15 the twisting in your abdomen.

16 On the way to the hospital, you start  
17 thinking of how you're going to handle the ER  
18 staff's not so subtle questions, questions that all  
19 but directly accuse you of being a drug dealer.  
20 You really want to be strong, but your agony is so  
21 great, you really just need some help with the  
22 pain.

1           Before you even arrive at the hospital, your  
2           swallowing becomes more difficult, and it feels  
3           like your throat is swelling shut. You're somewhat  
4           comforted that the car is dark enough that your  
5           loved one can't see how truly frightened you are of  
6           suffocating to death. When you arrive at the ER,  
7           you say a silent prayer that the next 72 hours will  
8           not be filled with the inexpressible horror of a  
9           doctor having to cut a hole into your windpipe  
10          because your throat has swollen shut faster than  
11          anyone anticipated.

12           Ladies and gentlemen, I am a poster child  
13          for demonstrating the true benefit of access to an  
14          easy-to-use on-demand therapy. For me and many  
15          other HAE patients, none of the above would have to  
16          be feared, endured or suffered. Safe, effective  
17          HAE therapy transforms lives, and access to a  
18          product like Firazyr would allow me to live a  
19          normal life, much the same as you live yours.

20           I urge the committee to vote yes for  
21          approval of and to expedite licensing of this safe  
22          and effective lifesaving HAE medicine. Thank you.

1 DR. KRISHNAN: Thank you.

2 Mr. Jacob Heis.

3 MR. HEIS: Good afternoon. My name is Jacob  
4 Heis. I do not have any financial ties to Shire,  
5 and I'm not a shareholder. And the U.S. HAE  
6 Association paid for my travel to be here today.

7 I am one of the so very many HAE patients  
8 who have lived their lives hoping to never have to  
9 face a medical emergency due to their disease. On  
10 May 15th, just a little over a month ago, this  
11 hope, my hope, was crushed.

12 It was 10:00 o'clock at night, and I was on  
13 my way to bed when I noticed the familiar sign that  
14 my throat was about to swell, a tingling, a feeling  
15 of thickness like swollen tonsils and the  
16 realization that simply swallowing was no longer  
17 easy. My father, girlfriend and I jumped into the  
18 car and headed to Denton, Texas hospital where the  
19 doctors are familiar with HAE. My girlfriend was  
20 driving as fast as she could. My dad sat right  
21 next to me, checking on the progress of my throat  
22 swelling. My dad noticed that I had begun to have

1 trouble breathing and realizing that the situation  
2 had quickly turned dangerous called the HAE  
3 Association's emergency line.

4           They recommended that we immediately call  
5 911 and have the paramedics meet us on the road. I  
6 vividly remember the terror we were all feeling as  
7 my dad placed the call and swelling progressed to  
8 the point that I could barely even swallow my own  
9 saliva. The HAEA staffed called ahead to Denton  
10 Presbyterian Hospital to explain my history of  
11 throat swellings, make sure the medical staff were  
12 ready for an emergency intubation, and as always in  
13 emergency rooms throughout the United States,  
14 stressed that HAE is not an allergy and that the  
15 usual antihistamines and epinephrine are not  
16 effective therapies.

17           Once we reached the hospital in Denton ER,  
18 the physicians attempted to call the HAE  
19 knowledgeable doctor for advice, but my throat  
20 began to close shut before the expert could be  
21 reached. The swelling had progressed to the point  
22 where ER doctors were unable to intubate me, and I

1 was rushed into the operating room. An emergency  
2 tracheotomy was performed, and then I was  
3 care-flighted to Dallas Presbyterian Hospital.

4 I spent many more days in the hospital and  
5 remember the joy when I was taken off the  
6 ventilator and I could finally breathe on my own.  
7 My father has hereditary angioedema, too, and it  
8 was a miracle that the stress of this did not land  
9 him in the hospital bed beside me.

10 Ladies and gentlemen, this entire ordeal  
11 could have been avoided by home access, easy-to-  
12 use, acute HAE therapy. We know from U.S. clinical  
13 trial and the experiences of European HAE patients  
14 that a shot of Firazyr at the first sight of my  
15 throat swelling would have avoided the panic drive  
16 down the highway at crazy speeds, the fear of dying  
17 on the side of the highway, a disfiguring  
18 tracheotomy, and an overwhelming experience from  
19 extended hospitalization, days without work, and a  
20 long, long recovery.

21 As you consider recommending approval of  
22 this new medicine, I hope you will consider that

1 the HAE attack I just described might have ended  
2 differently. Think about it. I came very close to  
3 being number 11 on the recent HAE death toll. I  
4 would have never been able to hug my father who  
5 feared of losing a son that night or simply hold my  
6 girlfriend. I urge the advisory committee to  
7 recommend approval. My future and the future of so  
8 many other HAE patients depend on it. Thank you.

9 DR. KRISHNAN: Great. Thank you very much.

10 Ms. Janet Long, we have one or two minutes,  
11 if you wanted to make some concluding comments.

12 MS. LONG: Thank you. I would just  
13 reemphasize that the HAE Association is fully  
14 behind individualized treatment plans for every HAE  
15 patient due to the unpredictability and variability  
16 of this disease. And we just want to emphasize  
17 again that we believe that every option should be  
18 available to every patient as far as their  
19 treatment.

20 So we thank you for your consideration of  
21 this product and for your time to let our HAE  
22 patients speak to you personally about how

1 important this is to us.

2 DR. KRISHNAN: Great. Thank you very much.

3 Next, we'll have Ms. Diane Dorman.

4 MS. DORMAN: Good afternoon. My name is  
5 Diane Dorman. I am vice president for public  
6 policy for the National Organization for Rare  
7 Disorders. I have no personal financial  
8 relationship with Shire. NORD does, however,  
9 administer four programs on behalf of Shire, two  
10 patient assistance programs and two travel  
11 assistance programs.

12 I'm here today not on behalf of Shire or  
13 their therapy, which is under consideration today.  
14 Rather, I am here on behalf of the millions of men,  
15 women and children in the United States affected by  
16 one of the 7,000 known rare diseases that in the  
17 aggregate affect 30 million people in the United  
18 States.

19 Rare disease research and the development of  
20 orphan therapies to treat them are unique in many  
21 respects. Patient populations are generally very  
22 small and geographically dispersed across the

1 world. And few researchers and biopharmaceutical  
2 companies are willing to take on the financial risk  
3 associated with this vital work. For those reasons  
4 and many more, NORD over the past 28 years has been  
5 dedicated to helping people with rare or orphan  
6 diseases and assisting the organizations that serve  
7 them. We are the primary non-governmental  
8 clearinghouse for information on rare disorders,  
9 and we are committed to the identification,  
10 treatment, and cure of rare disorders through  
11 programs of education, advocacy, research, and  
12 service.

13 Today, there are 375 orphan drugs and  
14 biologics that treat an estimated 200 rare  
15 conditions. Given that there are thousands more  
16 rare diseases without any specific treatments, it  
17 is easy to understand that there are millions of  
18 people who can only hope that one day someone  
19 somewhere will take on the significant financial  
20 risk to develop a therapy for their condition.

21 As you deliberate today, I ask that you keep  
22 in mind just a few things. Patients affected by

1 rare diseases are willing to take on a far greater  
2 degree of risk than those affected by more widely  
3 understood diseases affecting larger populations.  
4 Understanding the pathogenesis of rare diseases and  
5 the development of orphan biopharmaceuticals to  
6 treat them will only increase the medical  
7 community's understanding of diseases that affect  
8 far wider populations. And, number 3, there are  
9 few treatment options in the rare disease world  
10 because orphan drugs are highly specialized for  
11 very small patient populations. People affected by  
12 rare conditions and the doctors who care for them  
13 need treatment options just as those people dealing  
14 with conditions affecting far wider populations.  
15 Thank you.

16 DR. KRISHNAN: Thank you.

17 Dr. Henry Li, please.

18 DR. LI: Good afternoon, ladies and  
19 gentlemen and honored committee members. My name  
20 is Henry Li. For disclosure, I have participated  
21 in many clinical trials sponsored by Shire, Dyax,  
22 ViroPharma, and CSL Behring, all of them involved

1 in development of HAE treatment in the past few  
2 years. I also received consultation fees from  
3 Dyax, Shire, ViroPharma and CSL Behring in  
4 relationship to the trial development. I'm here  
5 today representing myself and my patients. I have  
6 not received any financial support to participate  
7 in this activity.

8 In the past more than 10 years, I've treated  
9 more than 60 HAE patients. I'm involved in more  
10 than 18 HAE-related clinical trials. Angioedema,  
11 especially HAE, is my area of special interest. I  
12 do share the frustration with my fellow physicians  
13 as well as the patient community for the lacking of  
14 safe, effective treatment for their HAE attacks.

15 The current available treatment options are  
16 not able to fully address the needs of the  
17 patients. From my personal experience, during my  
18 involvement in the icatibant clinical trials and  
19 also from my communication with my patients  
20 reviewing the clinical trial data, both from the  
21 safety and efficacy, and my corresponding with my  
22 physician colleagues throughout the country and

1 also around the world, I feel icatibant can  
2 certainly fill the need for the patients and  
3 especially the European experience for the past two  
4 years, which has been widely available like  
5 Dr. Maurer just pointed out. And many of his  
6 patients has used the drug. That feedback and our  
7 experience made me firmly believe icatibant is a  
8 great addition to HAE treatment.

9 One thing I'd like to bring to your  
10 attention is, last September, we had an  
11 international meeting, gathered around 58  
12 physicians experienced in treating HAE disease in  
13 Italy. And we have a consensus. A document is  
14 submitted for publication. And one conclusion I  
15 think we've reached is that, due to the  
16 unpredictability of HAE attacks, every patient  
17 should have a treatment available to them which is  
18 easy to use, safe and very effective. In addition,  
19 the ideal agent should be given to the patient,  
20 that the patient should have the ability to  
21 administer the drug themselves at the onset of  
22 attacks.

1 I believe icanibant has the potential of  
2 meeting all these needs. I sincerely hope this  
3 product will soon be available to the physicians  
4 and HAE patients in the United States. With that,  
5 thank you very much for your attention.

6 **Clarifying Questions for Sponsor (continued)**

7 DR. KRISHNAN: Great. Thank you very much.

8 The open public hearing portion of this  
9 meeting is now concluded, and we will no longer  
10 take comments from the audience. The committee  
11 will now turn its attention to address the task at  
12 hand, the careful consideration of the data before  
13 the committee as well as the public comments.

14 Before I have the FDA read the charge to the  
15 committee, I would want to give the opportunity to  
16 the committee members who were unable to ask for  
17 clarification to the sponsor. This goes back to  
18 the morning discussion. There were a few of you  
19 that wanted to speak that we were unable to  
20 accommodate at that time. I'll give you the  
21 opportunity now to ask for clarification to the  
22 sponsor, and then we'll actually go to the charge

1 of the committee and go through the various  
2 questions.

3 So the names of the committee members that  
4 had expressed an interest in asking questions were  
5 Dr. Tracy, Dr. Platts-Mills, and Dr. Shepherd. So  
6 let me just start in that order.

7 Dr. Tracy, do you have any questions for  
8 clarification to the sponsor?

9 DR. TRACY: Well, I had two questions. The  
10 first was really with regard to the blinding. I  
11 think that's been adequately addressed. The second  
12 question was really one of the choice of the  
13 abdomen versus, say, the arm or some other  
14 location. I'd just be interested in hearing any  
15 thoughts or rationales behind that.

16 DR. CAMMARATA: I don't think there's an  
17 exclusion of using other sites. That was really  
18 easy for patients to learn, a large area. They  
19 should avoid that area if they're having an  
20 abdominal attack and swelling of the skin. But,  
21 otherwise, that would be the area that's easiest  
22 for them to learn, learn how to self-inject.

1 DR. KRISHNAN: Any further questions,  
2 Dr. Tracy?

3 DR. TRACY: (Shakes head no.)

4 DR. KRISHNAN: Okay. And, Dr. Cammarata,  
5 when you answer the questions, if you could just  
6 state your name for the record, that'd be great.  
7 Thank you very much.

8 DR. CAMMARATA: Yes.

9 DR. KRISHNAN: Dr. Platts-Mills, I believe  
10 you had a question.

11 DR. PLATTS-MILLS: Yes. I'm very interested  
12 in the local reactions, and two things were  
13 mentioned this morning about the reactions.  
14 Firstly, we were shown a picture of what looked  
15 very much like a wheal and a flare, and that raises  
16 several issues. And, secondly, I think Dr. Maurer,  
17 when he was describing the technique for delivering  
18 the drug said it should be given deep below the  
19 porous tissues, including micelles.

20 So the question is these are wheals, but  
21 they do not have following late reactions. I think  
22 that's correct, that there's no description of a

1 late reaction following them, and clearly, there  
2 are no systemic reactions.

3 Does the company have any data suggesting  
4 that premedication can alter those reactions that  
5 would help us understand what the mechanism is? So  
6 if you see a wheal, the wheal could be due to a  
7 histamine-like product. It could be due to a  
8 codeine-like product which directly releases  
9 histamine from a micelle without any interaction  
10 with IgE, or it could be due because the product is  
11 an allergen.

12 I think there are no reasons for thinking  
13 that a decapeptide would be acting as an allergen  
14 when the question is, is it really acting in a  
15 codeine-like way directly causing release of  
16 histamine from micelles, and does the company know,  
17 have any information about that?

18 DR. CAMMARATA: Sue Cammarata from Shire.  
19 Yes, actually, we do have information. There are a  
20 couple different potential mechanisms that we have.  
21 One is that icatibant in very high concentrations  
22 can have a local agonist effect. So at the site of

1 injection, right, as you give it, you'll have very  
2 high concentrations so you can get warmth and  
3 redness from that. Also, there is some histamine,  
4 local histamine release at the injection site at  
5 those high concentrations, but it dissipates  
6 rapidly. And patients don't need any therapy at  
7 all.

8 I think, Dr. Maurer, you've had these kind  
9 of reactions. Maybe you're experienced, because  
10 from our clinical trial experience, there's been no  
11 need for any further intervention.

12 DR. MAURER: Sure. Marcus Maurer. So  
13 that's scientifically a very interesting question  
14 because it could link the micelle or allergy system  
15 to the bradykinin contact system. We've done a  
16 placebo-controlled prospective double-blind study,  
17 very small study, looking at the effects of  
18 Cetirizine, an antihistamine, on these local site  
19 reactions. And Cetirizine blocks about 50 percent  
20 of the swelling or whealing response. Also, when  
21 you look at the response of human skin micelles  
22 ex-vivo to icatibant, you do see histamine release,

1 prostaglandin release, and also cytokine release.

2           So in these concentrations that we're seeing  
3 here after local injection of icatibant, you do get  
4 micelle activation; at least, that's the most  
5 likely mechanism. That's independent of an  
6 IgE-dependent mechanism. That's just acting on the  
7 micelles and causing that release.

8           To put it into perspective, though, no one  
9 has ever not continued icatibant treatment because  
10 of that local site reaction. And with the new  
11 technique that we're learning about from our  
12 patients, many patients don't even experience that  
13 even more. It is good to know about this. For us  
14 as doctors, it's also good to learn about the  
15 mechanism because we can tell our patients, expect  
16 this to happen. This could happen. It's not bad.  
17 It won't last long. But we know why it's there and  
18 not to be afraid of allergic or anaphylactic  
19 reactions. But really to our patients, it's not a  
20 problem.

21           DR. KRISHNAN: Any additional questions,  
22 Dr. Platts-Mills?

1 DR. PLATTS-MILLS: No.

2 DR. KRISHNAN: Okay. I think the last  
3 question is to Dr. Shepherd.

4 DR. SHEPHERD: First, just a very quick  
5 question. What's the volume injected?

6 DR. CAMMARATA: Three ccs.

7 DR. SHEPHERD: Okay. My second question is  
8 broader, and that is, I realize that we're  
9 evaluating the data on the study group that is  
10 presented to us today. I have some concerns about  
11 post-approval use in patients that were excluded  
12 from this study, notably those with ischemic  
13 conditions.

14           Secondarily, although ACE inhibitors  
15 theoretically are going to be contraindicated in  
16 anybody with HAE, as we know, a lot of patients  
17 will present abruptly later in life and may well be  
18 on ACE inhibitors.

19           Does the company -- can I ask if the company  
20 has any plans with regard to labeling, with regard  
21 mainly to ischemic diseases where blocking the  
22 vasodilating effect of bradykinin might have

1 adverse consequences? And, secondly, the cutoff at  
2 age 16, one could anticipate off-label use in a  
3 younger population, whether the company has  
4 addressed these concerns.

5 DR. CAMMARATA: Eighteen.

6 DR. KRISHNAN: I'm sorry. So your questions  
7 are about exclusions.

8 DR. SHEPHERD: My question is what they plan  
9 to do with regard to labeling for those patients  
10 with ischemic diseases. I understand they would  
11 keep the 18.

12 DR. KRISHNAN: Dr. Badrul, did you want say  
13 anything before we have the sponsor respond to  
14 that?

15 DR. CHOWDHURY: I would just let the sponsor  
16 respond and see if we need to respond back, then we  
17 will.

18 [Laughter.]

19 DR. CAMMARATA: Thank you very much for  
20 that.

21 This is Sue Cammarata. I think I heard  
22 three different questions, but the first about

1 ischemia. Icatibant does not cause acute cardiac  
2 effects, so that's not a direct effect related to  
3 icatibant. However, there is this theoretical  
4 potential because bradykinin has this cardio  
5 protective effect. So we are looking at some  
6 wording so that physicians and patients are aware  
7 of the use or should not be used in ischemic  
8 conditions. I mean, we'll be working with the  
9 agency regarding that.

10 I think regarding pediatrics, at the present  
11 time, you're correct. We don't have information on  
12 children. So at this point in time, we are  
13 developing a program, and there is a plan to start  
14 trials to be able to understand dosing for  
15 children.

16 DR. KRISHNAN: It looks like Dr. Limb and  
17 Dr. Chowdhury, did you want to respond?

18 DR. LIMB: So just to add on to what  
19 Dr. Cammarata said -- this is Susan Limb, FDA -- we  
20 haven't discussed specific labeling with the  
21 sponsor. Certainly, if you as committee members  
22 feel like there's anything specific that you think

1 would help direct appropriate use of the product,  
2 then, certainly, we welcome your comments during  
3 the discussion and question period. Thank you.

4 DR. KRISHNAN: Dr. Shepherd, does that  
5 address the question?

6 DR. SHEPHERD: Yes.

7 DR. KRISHNAN: Are there any other committee  
8 members who have any specific questions for  
9 clarification to the sponsor at this point?

10 I'm sorry. Dr. Platts-Mills?

11 DR. PLATTS-MILLS: There's a minor issue  
12 that I thought about this morning, which is if the  
13 patients have it, then they have it with them and  
14 they can use it. Is it likely to be available in  
15 all emergency rooms so that it would then be  
16 available for use, or is that going to become a  
17 problem; that is, that although the drug is  
18 approved, it's not available at the place where it  
19 needs to be?

20 DR. CAMMARATA: I think that's one of the  
21 concerns that the patients and the families with  
22 HAE have since we already know that many hospitals

1 and clinics don't carry current therapies that are  
2 available for acute attacks.

3 DR. KRISHNAN: Dr. Greenberger.

4 DR. GREENBERGER: This came to my mind from  
5 this morning. For entry criteria for the three  
6 studies, did that include people that had failed  
7 acute treatment with one of the other two products  
8 that are available?

9 DR. CAMMARATA: Yes. Sue Cammarata again.  
10 It was not a -- there was no exclusion or inclusion  
11 regarding that. At the time of the FAST-1 and 2,  
12 those acute products were not approved, and in  
13 FAST-3, those products were approved after the  
14 study started. But that wasn't exclusion, and they  
15 could actually use those as rescue med, if needed.

16 DR. GREENBERGER: But my question is, say,  
17 for FAST-3, how many people already had failed a  
18 different product and then were entered into this  
19 study?

20 DR. CAMMARATA: As far as I know, none, but  
21 I don't know that we actually collected the  
22 information for that. That was not like an

1 inclusion that they failed previous therapy.

2 DR. GREENBERGER: I'm not trying to bring  
3 this morning back up, but that would cloud a clear  
4 interpretation. And you mentioned that one  
5 patient, I thought, got rescue C1 inhibitor.

6 Did not show that?

7 DR. CAMMARATA: Right. Patients had to be  
8 off C1 inhibitors for -- there's no restriction  
9 regarding ecallantide. Patients could not be on  
10 C1 inhibitors for five days prior to getting a dose  
11 with icatibant, but they could get those  
12 medications, for example, during attack as a rescue  
13 medication, so a few people did.

14 DR. GREENBERGER: So some could - you're  
15 telling me some people could have failed a  
16 kallikrein inhibitor and then be entered into  
17 this --

18 DR. CAMMARATA: No, they could not.

19 DR. GREENBERGER: They could not?

20 DR. CAMMARATA: Yes.

21 DR. GREENBERGER: Okay.

22 DR. KRISHNAN: Okay. Thank you.

1           So we will now proceed with the charge to  
2 the committee.

3                           **Charge to the Committee**

4           DR. LIMB: Good afternoon. So before we  
5 start the deliberations, I would like to provide  
6 some background on the laws governing FDA decisions  
7 of approval and non-approval before revisiting the  
8 questions for discussion and voting.

9           The Code of Federal Regulations, or CFR,  
10 states that FDA will approve an application after  
11 it determines that the drug meets the statutory  
12 standards for safety and effectiveness,  
13 manufacturing and controls, and labeling. Note  
14 that we are not discussing manufacturing and  
15 controls, which is product quality or the details  
16 of labeling today. While these requirements may  
17 affect decisions regarding approval, the discussion  
18 today is limited to safety and efficacy.

19           In terms of the standards for efficacy,  
20 they're shown here on this slide. The regulations  
21 specify the need for substantial evidence, meaning  
22 that efficacy has been demonstrated with certainty.

1           This slide shows the standards for safety.  
2           The regulation regarding the standards for safety  
3           can be summarized in four points. First, a  
4           submission does not have adequate tests to assess  
5           safety. Second, the product is unsafe. Third, the  
6           submission does not show that the product is safe.  
7           And fourth, there is insufficient information  
8           available to determine whether the product is safe.

9           Now, let us review the questions. There are  
10          a total of five. Two are intended for discussion,  
11          while the remaining three are voting questions.

12          Question 1 is a request to discuss the  
13          efficacy and safety data presented today.

14          Question 2 is the efficacy voting question.  
15          In addition to your vote, please provide a  
16          rationale for your vote and any additional comments  
17          that you may have on efficacy.

18          Question 3 is a voting question on safety.  
19          As for Question 2, please provide the rationale for  
20          your vote.

21          Question 4 is the final voting question.  
22          This question pertains to the overall risk-benefit

1 profile of icatibant and your approvability  
2 recommendation for this drug to the agency. Keep  
3 in mind that the standard for approval requires  
4 substantial evidence for both efficacy and safety.  
5 As such, your vote on Question 4 should be  
6 consistent with your votes from the previous two  
7 questions.

8 Question 5 is the last question. We will  
9 ask you to discuss the proposed self-administration  
10 of icatibant and the implications that this may  
11 have on safety and efficacy, if any.

12 I now turn the meeting back to Dr. Krishnan  
13 to open the discussion period. Thank you.

14 **Discussion and Questions to the Committee**

15 DR. KRISHNAN: Thank you, Dr. Limb.

16 We will now begin with the panel discussion  
17 portion of the meeting. Although this portion is  
18 open to public observers, public attendees may not  
19 participate except at the specific request of the  
20 panel. As Dr. Limb just mentioned, there are  
21 discussion questions and there are voting  
22 questions. I think we'll begin with the first

1 question, which is we were asked to discuss the  
2 efficacy and safety data for the drug.

3 Dr. Platts-Mills.

4 DR. PLATTS-MILLS: Can I ask a clarification  
5 question of Dr. Limb? Why isn't self-  
6 administration a voting question? Because,  
7 certainly, the way I see it, the self-  
8 administration is absolutely a really important  
9 part of this application.

10 DR. LIMB: So the questions were -- we felt  
11 that the efficacy question was the central  
12 question, and certainly self-administration may  
13 have an impact on efficacy. If you feel that that  
14 has some potential implication for approvability,  
15 then please provide your comments on that subject.

16 I don't know if Dr. Chowdhury has anything  
17 to add.

18 DR. CHOWDHURY: Just one small point to add.  
19 Again, we are asking for discussion on self-  
20 administration and not a question to that. The  
21 point I want to bring up here is the point that we  
22 discuss here is very important to us, and if we

1 raise any issues, we would like to hear that and  
2 take that into consideration in your decision  
3 making. Having a question as yes and no is rather  
4 irrelevant for this point. You can make the  
5 comment, and we'll certainly take into  
6 consideration. Thank you.

7 DR. KRISHNAN: I think, Dr. Posner, I saw  
8 your hand go up first, and then we'll head down  
9 there.

10 Dr. Posner?

11 DR. POSNER: Yes. I just had a technical  
12 question. Since during some of the earlier  
13 discussion it was pointed out this is for an orphan  
14 disease and an orphan drug, are there any special  
15 considerations that we give to efficacy on a  
16 particular population that's smaller than the  
17 regular cross-section of a drug that would be used  
18 by a lot more people?

19 DR. LIMB: So the regulations require the  
20 same standards for substantial evidence and  
21 efficacy. I think within that regulation there is  
22 some room for interpretation when we consider the

1 constraints of the disease itself and how these  
2 trials are conducted. So keep those in mind as you  
3 proceed with the discussion.

4 DR. KRISHNAN: Dr. Borish.

5 DR. BORISH: Yes. I just wanted to really  
6 repeat Dr. Platts-Mills' remark because there are a  
7 lot of people on this committee who treat this  
8 disease, and I don't think the agency does. And  
9 the agency is going to be weighing the labeling and  
10 whether to label it for self-administration. I  
11 just think it would be kind of useful for you to  
12 know what the opinions are of those of us on this  
13 committee who treat these patients and what we  
14 think, just as a vote, a voting item, of what we  
15 think of self-administration.

16 DR. CHOWDHURY: So to clarify, are you  
17 recommending that we ask a voting question for  
18 self-administration, or are you saying that your  
19 comments will be important for us to take into  
20 consideration?

21 DR. BORISH: I think it would be important  
22 for you to know what percent of doctors who treat

1 this disease think self-administration is going to  
2 be a really important part of the labeling  
3 requirements. That's a yes.

4 DR. CHOWDHURY: Understood.

5 DR. KRISHNAN: Is this related to the point,  
6 Dr. Greenberger? Please.

7 DR. GREENBERGER: I'm making the third  
8 comment in favor of making that a voting question,  
9 making question number 5 be voting.

10 DR. LIMB: Perhaps what we can do as a  
11 compromise is we can have discussion of the  
12 question as posed, and then if you would like to  
13 vote, we can take a vote.

14 DR. KRISHNAN: So since that's question  
15 number 5, how about we come back to that point?  
16 But it sounds to me that there's a number of people  
17 on the committee that would be in favor of making  
18 it a voting question.

19 Let me just go back to the order we have  
20 here.

21 Mr. Mullins, I believe you wanted to say  
22 something.

1 MR. MULLINS: Yes. I had a couple  
2 questions, but I had a point of clarification for  
3 the applicant. On page 17 of the extract of the  
4 briefing we were given by the FDA, there seems to  
5 be eight medical cases of women that were exposed  
6 to icatibant, and then it seems like the applicant  
7 reported there were seven cases.

8 So just a point of clarification, because  
9 one thing that we have is very limited information  
10 on subpopulations, and some of this information on  
11 subpopulations is very sparse. So as it relates to  
12 women that are pregnant or women that are engaged  
13 in fertility therapies, I want to fully understand  
14 the impact because there seems to be no  
15 adjudication on what happened with several of the  
16 women that were exposed to icatibant.

17 DR. CAMMARATA: The dossier was submitted  
18 with the data cut from last year --

19 DR. KRISHNAN: Do you want to just say your  
20 name again? I'm sorry.

21 DR. CAMMARATA: Sue Cammarata. I'm sorry.  
22 The dossier was submitted in February with

1 the data cut last fall, and with all clinical  
2 trials and since the drug is on the market already  
3 globally, we receive information about -- potential  
4 information about things like that over time, and  
5 they accumulate over time. So there are numbers;  
6 you could take a data cut of what was submitted at  
7 the time, a dossier versus the information that's  
8 occurred up to now, and maybe next week I might  
9 have another report. So that's where the numbers  
10 change over time.

11 So I believe that the exposure data that  
12 Dr. Bajwa talked about already, the seven patients  
13 that we know about, were five in clinical trials  
14 and two postmarketing, and that was of May 17th.  
15 So that's the information she relayed previously.

16 MR. MULLINS: Do you have any graphs or any  
17 data that I could see? Because it seems -- yes.

18 DR. CAMMARATA: Slide up. All we have is  
19 the summary of what happened with the patients.  
20 And there are seven pregnancies. There were five  
21 healthy newborns, one newborn who we're waiting to  
22 get follow-up. There's one elected termination,

1 and again another one while we're waiting for  
2 follow-up.

3 MR. MULLINS: Okay. So the data that we  
4 were given by the FDA, that's a different set of  
5 statistics?

6 DR. CAMMARATA: So, as I said, it looks  
7 over -- there was one patient, I believe, that was  
8 double counted in the numbers that were -- is that  
9 correct -- from the FDA? Yes. So there was one  
10 number that was double counted, and we clarified  
11 that. So it was a patient that was a placebo  
12 patient that was included in that number.

13 MR. MULLINS: My next question is, this  
14 committee is being asked to make assumptions,  
15 heterogeneous assumptions based on homogenous  
16 information. And I struggle with that because the  
17 population -- the HAE population is quite different  
18 than the population that was in the trial sample  
19 and the trial population.

20 Could you address how you were able to make  
21 assumptions about efficacy and safety within such a  
22 homogenous population?

1 DR. CAMMARATA: Yes. The clinical trials  
2 for icatibant, you're correct, that most of the  
3 patients, for example, were Caucasian and about  
4 two-thirds were female. When we looked at the  
5 database --

6 MR. MULLINS: Also, the weight issue, they  
7 were very similar. The mean weight was --

8 DR. CAMMARATA: We did assessments looking  
9 at all of the patients we did have, for example,  
10 the non-white patients, the male patients, which  
11 was about a third of the population and across  
12 weights. And when we looked -- regardless of all  
13 those subgroups, the efficacy for icatibant is  
14 consistently the same.

15 However, we recognize that it's a small  
16 database because it is an orphan disease and a rare  
17 disorder, so it's difficult to always get the  
18 breadth of patients that you would like in a  
19 clinical trial. But we do find that from the  
20 outcomes that we have, the efficacy is similar for  
21 icatibant consistently.

22 MR. MULLINS: My concern is that we'll be

1 making decisions about a patient population that  
2 might be reflected in your studies. And just based  
3 on the ethics of that, I want to understand how you  
4 arrived at that decision-making process.

5 DR. CAMMARATA: Sure. I can show you the  
6 outcomes of the data that we have on the patients,  
7 male, female; for example, the groups that you're  
8 looking for, if you're interested. We do have  
9 those outcomes for non-white, by weight, and by  
10 gender, if you're interested. Again, it's a small  
11 database, but I can show you the icatibant outcome  
12 and efficacy in those groups.

13 DR. KRISHNAN: Mr. Mullins, did you want  
14 them to show those data?

15 MR. MULLINS: Yes, I did want to see that.

16 DR. CAMMARATA: So if we could have the time  
17 to onset of symptom relief by subgroups? Okay. So  
18 if we can show time to onset of symptom relief for  
19 the Caucasian patients, and then we'll go to the  
20 non-Caucasian patients.

21 Slide up, please. We have time to onset of  
22 symptom relief. If you remember, that was the

1 primary endpoint that we used, and this is for the  
2 patient population with icatibant showing an onset  
3 of 2 hours versus the 10 and 12 hours placebo and  
4 versus tranexamic acid.

5 Next slide. So we'll be again  
6 showing -- these are all the Kaplan-Meier curves  
7 showing you all the patients; again, small numbers.  
8 For the non-white population, we had an outcome of  
9 time to onset of symptom relief for this population  
10 of 1.5 hours versus the placebo patients of  
11 8 hours.

12 Next, we're going to look at females. Time  
13 to onset of symptom relief, again, the primary  
14 endpoint for females was a median time of 2 hours  
15 versus placebo at 6, and 9 hours of tranexamic  
16 acid. So, again, rapid onset for icatibant fairly  
17 consistently at two hours. And then when you look  
18 at time to onset for males, time to onset of  
19 symptom relief for males, again, rapid onset with  
20 icatibant at 3.5 hours and with placebo at  
21 31 hours, tranexamic acid at 17 hours.

22 Then the last I'll show you by weight.

1 It's, again, same Kaplan-Meier curve. Time to  
2 onset of symptom relief for the patients that are  
3 less than 75 kilograms, again, time to onset was  
4 2 hours for icatibant versus the 6 for placebo, and  
5 9 for tranexamic acid. And then for the patients  
6 that were heavier, above 75 kilograms, icatibant,  
7 the mean in the subgroup was 3 hours versus placebo  
8 of 22.5, and tranexamic acid of 15.

9 So icatibant is very consistent in having  
10 its rapid onset compared to the comparator groups.

11 MR. MULLINS: Did you say for the group that  
12 was over 75 kilograms it was 3 hours versus 1.5?

13 DR. CAMMARATA: Yes, versus --

14 MR. MULLINS: Okay.

15 DR. CAMMARATA: -- versus I think it was  
16 two.

17 MR. MULLINS: Two?

18 DR. CAMMARATA: Yes.

19 MR. MULLINS: Versus two. Okay.

20 Then my last question, I wanted to  
21 understand, it seems like you started out with  
22 your -- I wanted to understand your prescreening

1 process because it seems like you started with a  
2 huge 792 possible patients, but then it dwindled  
3 down to actually 236, 225 that were actually  
4 involved in the trial. So can you comment on how  
5 you think that process was conducted so that we  
6 ended up with a patient population that's reflected  
7 in very similar health profiles?

8 DR. CAMMARATA: For all three  
9 studies -- because, as you heard today from the  
10 patient groups, HAE patients can't predict  
11 necessarily when they're going to have an attack.  
12 They may have -- some may be fairly regular; some  
13 may be more intermittent. So from doing a clinical  
14 trial, you can't predict ahead of time that they  
15 can come in on a particular day.

16 So what all of these trials did is that all  
17 the patients were prescreened, so the physicians  
18 that were in clinical trials at clinical study  
19 sites would invite any patients that were eligible  
20 and met the enrollment criteria to see if they  
21 would be interested in participating. So those  
22 patients were prescreened. And then patients, when

1 they had an attack that met -- for example, it had  
2 to be moderate to severe to be actually dosed.  
3 When those patients had an attack, they would come  
4 back to the clinic. So they would be -- basically,  
5 enrollment would go as patients had an attack. And  
6 so that's how patients were entered into the trial  
7 is when they had an attack.

8 DR. KRISHNAN: Okay. Thank you very much.

9 I think, Dr. Chowdhury, at some point, you  
10 wanted to make a clarification or say something on  
11 behalf of FDA.

12 DR. CHOWDHURY: Yes, thank you very much. I  
13 would like to go back to the request for asking a  
14 question on self-administration. And we will ask  
15 the question because that's the request that came.  
16 The question will be something like do the data  
17 support the self-administration of icatibant, and  
18 we'll try to put it up on the screen in a timely  
19 fashion so that it can go up for voting. Thank  
20 you.

21 DR. KRISHNAN: Great. Thank you.

22 Are there other discussion points among the

1 committee members regarding the safety or efficacy  
2 of icatibant?

3 [No response.]

4 DR. KRISHNAN: So hearing none, then I'm  
5 going to suggest we proceed -- one second. I'm  
6 sorry. I apologize. There are a few committee  
7 members who wanted to ask a few more questions, I  
8 believe.

9 Dr. Stone?

10 DR. STONE: Yes. I mean, you just sort of  
11 answered it. So the only question I had was the  
12 self-administration trial. When is that scheduled  
13 to wrap up? That's still ongoing?

14 DR. CAMMARATA: The self-administration  
15 trial is basically almost basically done. We'll be  
16 having a study report, because the data cut we had  
17 was for 56 patients, but, subsequently, other  
18 patients have enrolled. And that will be shutting  
19 down over the summer with a report later on this  
20 year.

21 DR. KRISHNAN: Can I just ask, just to build  
22 on Dr. Stone's question to the FDA, if it is a

1 discussion point and then perhaps maybe changes to  
2 our voting question, yet one of the studies the  
3 sponsor is doing to directly address this is not  
4 yet available, could you comment on the committee's  
5 charge to address and discuss that issue if the  
6 data that were specifically designed to address  
7 this aren't quite fully mature yet for us to look  
8 at?

9 DR. CHOWDHURY: Well, I think we need to  
10 take into consideration what is available now and  
11 decide based on the data that is available. And if  
12 you think the data is available, then, of course,  
13 you'll be voting yes. If you think it is not, then  
14 you go in that direction and tell us what we need  
15 to look at further for addressing the negative  
16 recommendation if that's your recommendation.

17 DR. KRISHNAN: Great.

18 Dr. Stone, does that address the question  
19 you had originally asked?

20 DR. STONE: (Shakes head yes.)

21 DR. KRISHNAN: Let's see. I think we had  
22 Dr. Platts-Mills, and then we had Dr. Mauger.

1 Dr. Platts-Mills?

2 DR. PLATTS-MILLS: Now, I was actually  
3 thinking of a question about minority and whether  
4 the HAE Association could actually tell us minority  
5 figures for the disease. That is, is this disease  
6 more common in one group of the population or not?  
7 Because, given its rarity, it would be extremely  
8 difficult to get any data about minority groups,  
9 especially if they're more common or less common.

10 DR. KRISHNAN: Sure. Maybe we can ask  
11 Ms. Janet Long to perhaps comment on what her group  
12 may know about prevalence of this disease among  
13 minorities, or perhaps what kinds of prevalences  
14 you have of ethnicities and race in your  
15 organization.

16 Is there a microphone? Perhaps we could  
17 have you use --

18 MS. LONG: Thank you. Unfortunately, there  
19 has been no real epidemiological study done on HAE  
20 in the United States. We know that it does cover  
21 all races. There is none that are not HAE  
22 patients. As far as our association, we haven't

1 done a breakdown of the different races that have  
2 HAE in the United States.

3 I don't think there has been anything in the  
4 literature that comes to my mind that addresses any  
5 differences in how this disease affects anyone from  
6 any different range of any race. So I would say  
7 that from my own viewpoint -- I'm not a physician,  
8 but I would say that we have no literature and no  
9 findings in the HAE Association that this disease  
10 doesn't cover everyone equally, broadly, race,  
11 gender, creed.

12 DR. KRISHNAN: Great. Thank you.

13 Dr. Borish.

14 DR. BORISH: There are some data on that. I  
15 mean, given its autosomal dominance, it has a very  
16 strong founder effect. I mean, it's known which  
17 ship, for example, in the Boston area, which  
18 pilgrim ancestor came over and brought the HAE to  
19 Boston. And I suspect a lot of the people who  
20 testified earlier, if you went back a few  
21 generations, you'll find your cousins. And it  
22 tends to be in that Anglo-Saxon and I think the

1 Dutch -- there's some Dutch ancestor who moved to  
2 Minnesota or something. There really is a very  
3 strong Caucasian preference for this disease.

4 DR. KRISHNAN: So one of the things at least  
5 I'm hearing from a variety of people on the  
6 committee is the fact that we have modest numbers  
7 of patients enrolled in these studies. It's a rare  
8 disease. It's difficult to get very large numbers,  
9 but even so, we have a relatively homogenous  
10 population. Then we wonder about the extent to  
11 which results may be applicable to others once the  
12 drug is approved.

13 Perhaps I might just suggest for a moment  
14 that one approach might be to ask the sponsor to  
15 maintain a registry so that if the study drug is  
16 approved, that there's an opportunity to collect,  
17 if anything, safety data or to collect additional  
18 data about its use by various practitioners, so we  
19 have a denominator, if you will, to start to be  
20 able to understand the epidemiology of its use and  
21 perhaps adverse events.

22 I don't know if that's of interest to others

1 on the committee, but I keep hearing questions  
2 about the lack of diversity among the study  
3 patients, and whatever epidemiology data we have  
4 seems limited compared to other conditions,  
5 potentially.

6 Any discussion around that point?

7 Dr. Posner.

8 DR. POSNER: I'd like to second that. It  
9 was one of the suggestions I was going to make at  
10 the end, that a registry be maintained, and  
11 particularly with the European use of it, which is  
12 far more brisk right now, to get that going.

13 I'd also like to point out with the minority  
14 population and the numbers, having heard how  
15 difficult it is to diagnose this disorder, I  
16 wouldn't count the minorities as being  
17 underrepresented in the population because, again,  
18 when we look at minority healthcare in this country  
19 and the ability to be diagnosed at the appropriate  
20 centers, there may be a lot of minorities that do  
21 have this disorders that just die.

22 DR. KRISHNAN: Right. So this may help

1 understand the numbers better. The other  
2 opportunity for registries is that it may help set  
3 the sponsor up for future studies because then you  
4 have a list of people. But I'm assuming the  
5 sponsor may have thought about this or may already  
6 have a registry.

7 Maybe you could comment from your  
8 perspective.

9 DR. CAMMARATA: We already have an outcome  
10 survey that's already started. Every country where  
11 we have launched, we've started that outcome  
12 survey. So if approved in the U.S., we plan to  
13 start that same type of survey here in the U.S.,  
14 also, for patients to participate.

15 DR. KRISHNAN: So just to clarify, what  
16 would be an outcome survey? I was thinking more  
17 about if the drug is prescribed to an individual,  
18 that person's name and contact information perhaps  
19 gets entered into a registry.

20 Are you talking about something more  
21 voluntary or something along the lines of --

22 DR. CAMMARATA: It's information for

1 physicians and patients who have hereditary  
2 angioedema, when they have treatment -- and also  
3 those patients who are not on treatment -- they can  
4 register. And there's information like adverse  
5 event data collected. There's other information  
6 that's being collected. So we've started that in  
7 other countries and would continue that in the U.S.

8 DR. KRISHNAN: Yes. I think, though, if we  
9 make it voluntary in that respect, you may not get  
10 the full denominator of people on therapy. One  
11 consideration could be to formalize that process  
12 some more and actually require a registry of people  
13 to whom this has been prescribed. This will  
14 provide us, I think, a lot of information that  
15 could clarify the points being discussed.

16 So let's see. I think Dr. Mauger,  
17 Dr. Portnoy, and then I believe Dr. Borish.

18 Dr. Mauger.

19 DR. MAUGER: This is, I guess, a procedural  
20 question. I had earlier asked whether the FDA had  
21 an opinion about what was the appropriate parameter  
22 in which to judge efficacy in these studies.

1 Obviously, there was a priori defined primary  
2 outcome for which there's statistical evidence, and  
3 you had turned that around and said, well, what do  
4 you think.

5 So now my question is when should I give my  
6 opinion on that? If that appropriate for -- that's  
7 not quite under what you've got here as Question 1.

8 Is this a time to discuss that, or should we  
9 wait until we get to the voting?

10 DR. LIMB: Please discuss now.

11 [Laughter.]

12 DR. MAUGER: The reason I'm asking is  
13 because this is going to give away my vote. So if  
14 it would be preferable until my explanation of my  
15 vote, I would do that.

16 DR. CHOWDURY: I just wanted to jump in  
17 here. The choice is really yours. If you have  
18 some issues that you think are important for  
19 everyone to hear and would impact the decision  
20 making in some ways, then please feel free to  
21 discuss it now. If you think otherwise, you can  
22 hold up. It's up to you, though.

1 DR. ROSEBRAUGH: I'm going to jump in a  
2 little more. Actually, I think you should bring up  
3 your opinion because there may be people on the  
4 panel that disagree with it, and then we would have  
5 a lively discussion, and that's important to us to  
6 hear.

7 DR. MAUGER: Okay. So there are two issues.  
8 One that I think is very important that I know was  
9 addressed and sort of said, well, that's the best  
10 we can do, and this was the issue of unblinding.  
11 The reason I bring it up is that I'm puzzled by the  
12 results of the comparison of the FAST-1 to the  
13 FAST-3.

14 If I look at why there seemed to be little  
15 evidence of a treatment effect in FAST-1, it's not  
16 because the icatibant didn't work, it's because the  
17 placebo appeared to work. Either that means that  
18 the population that was selected is one that was  
19 going to improve anyways regardless of treatment,  
20 or it could be that there really is legitimate  
21 placebo effect and that there was an apparent  
22 improvement of the placebo group that was just due

1 to participation in the study and not because of  
2 anything else.

3 If that's the case, then that makes the  
4 results of FAST-3 potentially questionable because  
5 we now feel pretty confident there was unblinding  
6 amongst the patients who got the active, or we  
7 think that that's a serious potential problem. So  
8 that's one concern that I have.

9 The other has to do with what's the  
10 parameter on which to judge efficacy. What I would  
11 not want to see come out of this at the end would  
12 be a marketing that said that icatibant reduced the  
13 time till onset till -- excuse me. I would not  
14 want to see the claim made that icatibant reduced  
15 the time to onset of symptom relief by 18 hours. I  
16 think that that metric is artificially driven by  
17 the times at which the data was collected. I think  
18 that's reflected by the width of the confidence  
19 intervals.

20 What I am convinced by, though, is what  
21 percentage of patients have experienced onset of  
22 relief within, say, the first eight hours. I think

1 that is very relevant, and I think that's actually  
2 quite clearly demonstrates efficacy of icatibant  
3 over placebo, at least in the FAST-3 trial.

4 DR. KRISHNAN: So I have a question,  
5 Dr. Mauger. So the idea of unblinding, which I  
6 think we can safely assume occurred given the very  
7 high prevalence of a local site reaction, how would  
8 unblinding lead to a negative study? In the sense  
9 that if the unblinding were to lead patients who  
10 received the drug, and they know they received the  
11 drug, to report benefit, you would expect, if  
12 anything, benefit to be exaggerated.

13 DR. MAUGER: That's right. I'm sorry. I  
14 lost the question, though.

15 DR. KRISHNAN: I thought I heard you  
16 say -- and it's possible I didn't hear the whole  
17 thought -- that unblinding may have been  
18 responsible for the lack of benefit in FAST-1, lack  
19 of significant benefit in FAST-1.

20 DR. MAUGER: Well, we don't have from FAST-1  
21 data on whether there was likely to have been  
22 unblinding. One would think that it was similar.

1       What I said is we don't have data on the reporting  
2       of local symptoms in FAST-1, but probably it was  
3       similar. And so if there was an unblinding effect,  
4       presumably, it was the same in both trials, but we  
5       just don't have evidence on that.

6                What I was really commenting, though, is  
7       trying to deduce an explanation for the FAST-1 lack  
8       of effect and whether that was possibly due to  
9       selection of the incorrect population that was  
10      going to improve within 10 hours anyway or whether  
11      there was placebo effect.

12              The other comment I would have here is that  
13      I also buy the single symptom relief score better  
14      than I do this composite of three, partly because  
15      we're mixing up two different populations and  
16      that's the cutaneous group as well as the abdominal  
17      group. And this VAS-3 score is weighted toward  
18      cutaneous because it's got three parameters in it,  
19      and two of them are cutaneous, and one of them is  
20      abdominal. So I think that makes for a potentially  
21      biased measure or differentially biased outcome  
22      measure, depending on which population we're

1 talking about.

2 DR. KRISHNAN: Great. Let me just look at  
3 our list here. I think Dr. Portnoy is next.

4 DR. PORTNOY: Yes. Obviously, our task here  
5 is to decide whether we believe this is a safe and  
6 effective drug, and the testimonials were certainly  
7 moving and we listened to them carefully. But we  
8 want to be careful not to unleash upon the public a  
9 product that may not be safe and effective, even if  
10 the people who are using it are desperate for  
11 something that they can use to give them hope for  
12 their disease.

13 So I just want to make clear that this  
14 group, at least my -- I feel very strongly that I  
15 want to be as impartial about evaluating the data  
16 as possible to make sure that we're doing the right  
17 thing.

18 In terms of the disease itself, I wanted to  
19 expand on what Dr. Borish said about the founder  
20 effect, and that is that there are a small number  
21 of genetic defects that lead to this disease. And  
22 it seems to me that a number of people who have

1       been enrolled in these trials may all be members of  
2       the same family and may, in fact, have the same  
3       identical genetic defect. And I'm wondering  
4       whether there are differential responses to this  
5       treatment depending on which specific genetic  
6       effect has caused that family's hereditary  
7       angioedema and whether that's something that's been  
8       looked at and whether there are plans to look for  
9       the pharmacogenetics of the response to this drug,  
10      given the fact that the genetic variability is  
11      fairly limited.

12             DR. KRISHNAN: I guess, is that a question  
13      to the sponsor then?

14             DR. PORTNOY: If that's okay, or at least  
15      I'd like to recommend that that be done if it's not  
16      in the planning.

17             DR. KRISHNAN: Sure. Maybe the sponsor  
18      could respond to that.

19             DR. CAMMARATA: This is Sue Cammarata.  
20      There are over 200 various mutations related to  
21      this, and we do not have that information. We did  
22      look at type, like Type 1 and Type 2, but we don't

1 have any information beyond in the way you're  
2 describing it.

3 DR. KRISHNAN: So just so the committee  
4 members realize, we have a list of Dr. Borish,  
5 Dr. Jacoby. I'm not sure I can read --  
6 Dr. Strahlman, Dr. Platts-Mills, and  
7 Dr. Greenberger. That's the list we have right  
8 now, so let me go to Dr. Borish.

9 DR. BORISH: Both as reassurance for the  
10 question again about the possible nonresponsiveness  
11 in certain ethnic groups and Dr. Krishnan's request  
12 for possibly a registry and Dr. Portnoy's comment.  
13 This disease isn't asthma, which is probably, as  
14 you know, a 100 diseases all thrown together into  
15 one lump term.

16 This is a homogenous disease caused by a C1  
17 inhibitor deficiency, where there's overproduction  
18 of bradykinin that binds the bradykinin Type 2  
19 receptor. Two hundred genes, that's all the exact  
20 same phenotype. Yes, there's heterogeneity in  
21 frequency and severity, but that heterogeneity  
22 doesn't change. So I just can't think of any

1 mechanism that of concern of thinking that there  
2 might be responders and nonresponders.

3 Now, there's an issue when we were  
4 discussing the C1 inhibitor drug because, arguably,  
5 some of these mutations, most of the produce stop  
6 codons and the protein is broken down and is  
7 destroyed, and, thus, the nucleus. There's a  
8 question whether some of the mutations might  
9 produce a protein that could act as an autosomal  
10 dominant negative competitive inhibitor, and then  
11 there might have been responders and nonresponders.  
12 But I just don't see a mechanism for that with this  
13 particular target.

14 DR. KRISHNAN: Thank you.

15 Dr. Jacoby.

16 DR. JACOBY: I just wanted to comment on the  
17 apparent efficacy of the placebo in the FAST-1  
18 trial, and I thought this was what Dr. Greenberger  
19 was getting at with his question this morning.

20 In comparing the FAST-1 trial to the FAST-3  
21 trial and looking for why there would be a  
22 difference, it seems as though one of the major

1 differences was about a nearly five-hour difference  
2 in the time between onset of symptoms and delivery  
3 of either drug or placebo.

4           So it's a matter of when -- one possibility  
5 is that it's a matter of when you start measuring  
6 the time to resolution. So, to me, that's less of  
7 an issue. And one might argue that it might be an  
8 argument in favor of early administration of drug,  
9 although it doesn't seem as though there's much  
10 difference in the treatment group.

11           DR. KRISHNAN: Great. Thank you very much.

12           Dr. Strahlman.

13           DR. STRAHLMAN: Yes. I'd like to return to  
14 the question of patient registries, which was  
15 suggested. And the purpose of that, I believe your  
16 intent behind that was to ensure that we capture  
17 safety information or the safety information would  
18 be captured. There are issues, however, with  
19 patient registries that I would like to hear from  
20 the committee on how they feel about that. One are  
21 patient privacy issues, and secondly, sort of the  
22 bureaucracy and limiting access, both of which will

1 be of concern for this medicine.

2 To maybe get some clarification on this  
3 since it is a rare disease -- like you say, it's  
4 not asthma; we don't have hundreds of thousands of  
5 patients -- I wonder if the sponsor could clarify,  
6 based on the surveys they do in each country, if  
7 they have a sense, from the capture of that  
8 information and also their marketing data, if  
9 they're actually getting most of the information.  
10 I'm not sure we have that information, but it might  
11 be useful if we did. It might inform us on our  
12 request for a registry.

13 DR. KRISHNAN: So I'm hearing several  
14 questions. Let me just -- please go ahead, but I  
15 just wanted to amplify the concept that the  
16 registry is, I think, one idea that gives you a  
17 denominator to be able to identify adverse events  
18 in a more systematic way. But the other way really  
19 is actually to build a robust dataset from which  
20 you can then enroll patients in trials.

21 The CF community has done that extremely  
22 well, and the number of CF patients is actually

1 about in the same range as what we're talking about  
2 here. There about 20,000 CF patients, and there's  
3 no one that would disagree that they've done that  
4 really well in capturing a population and  
5 repeatedly studying them and moving the ball  
6 forward.

7 So I think it's not just a safety issue. It  
8 actually provides, I think, a mechanism to learn  
9 science and help patients.

10 DR. CAMMARATA: But the CF registry is  
11 voluntary.

12 DR. KRISHNAN: It is voluntary, but it turns  
13 out to be pretty highly subscribed to because you  
14 get access to trials you would not otherwise have,  
15 and there's other benefits to enrolling. I don't  
16 want to get too far into the CF registry in today's  
17 discussion, but it's worth looking into. It's a  
18 good model, actually, for studying rare disease.

19 DR. CAMMARATA: Shire as a company, Shire  
20 HGT, works in rare diseases, so we have a number of  
21 outcome surveys that are worked for other  
22 indications, other areas. And as I mentioned, it's

1 starting out here with the population for the HAE  
2 community. So we are just starting to roll that  
3 out. That started in Europe, and it's really only  
4 picked up significantly in the last six months. So  
5 our intent is to do that in every country,  
6 including the U.S.

7 At the moment, we have approximately  
8 30 percent of patients who are on icodec  
9 enrolling, and that number is increasing. It's  
10 really jumped up significantly in the last six  
11 months, and I think particularly in Europe where  
12 self-administration was approved. So we intend to  
13 continue doing that to get information about the  
14 safety, and we do ask other questions for the  
15 patients as well as information about patients who  
16 have HAE in general.

17 DR. KRISHNAN: Okay. I think -- let's see.  
18 Dr. Platts-Mills.

19 DR. PLATTS-MILLS: Thank you. I just wanted  
20 to make a minor point about what David said earlier  
21 about the issue of VAS-1 versus VAS-3. The  
22 thing -- that what we saw was a breakdown of the

1 cutaneous versus abdominal, and it seemed very  
2 consistent; that is that even though you could  
3 argue about one way of looking at it or another, it  
4 seemed that whether you looked at it as abdominal  
5 or looked at it as cutaneous, you were getting the  
6 same result, certainly, in FAST-3.

7 DR. MAUGER: Right. If I expressed that I  
8 was skeptical about the results because of what I  
9 was saying, I didn't mean to. I find the results  
10 very convincing. It's just that I actually find  
11 the single ones more convincing than the VAS-3.  
12 But I agree with you completely, that the results  
13 were consistent and convincing.

14 DR. KRISHNAN: Okay. Dr. Greenberger.

15 DR. GREENBERGER: Could the sponsor state  
16 what is in the placebo injection and the volume for  
17 FAST-3 and 1? I missed it.

18 DR. CAMMARATA: Sue Cammarata. Yes, it's  
19 3 ccs. It's actually the same vehicle that the  
20 icatibant is in.

21 DR. GREENBERGER: Could you state what's in  
22 the vehicle?

1 DR. CAMMARATA: Let's see. I don't know  
2 what's in the vehicle, but Jim Weston may know his  
3 vehicle.

4 DR. WESTON: Jim Weston, senior director of  
5 regulatory at Shire. It's an acetate buffer. It's  
6 a 5.5 acetate buffer, pH 5.

7 DR. KRISHNAN: Okay. Any further -- I think  
8 we have run through the list here.

9 Any other additional committee members have  
10 questions or comments they want to make about  
11 safety or efficacy?

12 Mr. Mullins?

13 MR. MULLINS: I had a question about  
14 postmarketing studies in the EU among the patient  
15 population that self-administered. It seems to be  
16 that's a small portion of the population, and we're  
17 preparing to make a decision on efficacy and safety  
18 on the population that self-administers. So I  
19 wanted to understand do we have any data from the  
20 EU because right now from the data we have on  
21 phase 2 and phase 3 is very limited, only 26  
22 percent self-administered.

1           So do you have any information about  
2 complications and issues and postmarketing analysis  
3 from the EU?

4           DR. CAMMARATA: This is Sue Cammarata. It  
5 appears you're asking about postmarketing safety  
6 reporting; is that correct?

7           MR. MULLINS: Yes, among patients that self-  
8 administered icatibant.

9           DR. CAMMARATA: Yes, we have a little bit of  
10 information because that just launched officially  
11 as a label change in earlier this year, so we do  
12 have a little bit of adverse event reporting. But  
13 specifically for self-admin is what you're looking  
14 for?

15           Dr. Bajwa, if you can comment.

16           DR. BAJWA: Naghmana Bajwa, global  
17 pharmacovigilance and risk management. As  
18 Dr. Cammarata mentioned, we have had this registry  
19 ongoing since the approval in Europe in 2008, and  
20 shortly after that, the registry was implemented.  
21 We have over 30 percent of patients enrolled in the  
22 registry that are being treated in those countries.

1 Out of those, we have 117 patients who have had  
2 documented attacks and treated with icanitabant. The  
3 enrollment has picked up quite a bit. We have  
4 ethnicity data on that as well.

5 MR. MULLINS: Look at efficacy and safety  
6 information on the population. Do you have a slide  
7 on that?

8 DR. BAJWA: Could I see the ethnicity data,  
9 please?

10 So we collected on ethnicity as well in  
11 Caucasians, non-Caucasians, and a few patients that  
12 we have missing information. We do have over eight  
13 patients treated with icanitabant in non-Caucasian.  
14 That is the breakdown in blacks, Orientals, Asian  
15 and other mixed kind of races. And the safety  
16 profile seems consistent with what we saw in  
17 clinical trials.

18 MR. MULLINS: I'm not just concerned about  
19 ethnicity. I'm concerned about just overall safety  
20 and efficacy amongst the population that self-  
21 administered.

22 Do you have data on that?

1 DR. CAMMARATA: Can we please have the slide  
2 summarizing the postmarketing safety reports? And  
3 if you have anything on the self-admin, please.

4 That information is rather limited because  
5 it just launched.

6 DR. BAJWA: So in terms of self-admin, we  
7 have 180 attacks that have been treated as self-  
8 admin. Overall, the dataset is collected within  
9 the postmarketing. The total number of events we  
10 have received is 25 of 13 patients, and that  
11 includes patients on self-admin.

12 MR. MULLINS: I just feel that's a pivotal  
13 question for this committee. So I think any  
14 relevant information that we have on self-  
15 administration I think is vital for us to make a  
16 well-informed decision on efficacy and safety of  
17 this therapy.

18 DR. CAMMARATA: Could I ask Dr. Maurer to  
19 comment since he has 60 patients that have been  
20 getting self-admin?

21 DR. MAURER: Marcus Maurer. We're not the  
22 only center that has been treating patients that

1 self-inject for the past years. We share that  
2 experience with many other centers, and a lot of  
3 that information has gone into the outcome survey.  
4 So a lot of the patients that are documented there  
5 for safety and adverse events are actually self-  
6 admin patients.

7 Now, out of hundreds of attacks that have  
8 been treated by patients themselves using this  
9 drug, in more than 50 patients, we see essentially  
10 the same safety and efficacy profile. If at all,  
11 then patients report that it's working better  
12 because, largely, they can treat earlier. An  
13 early-treated attack is a well-treated attack.  
14 They don't have to endure the pain, and the  
15 swelling doesn't progress so much. And if at all,  
16 they're not treating as much so they actually use  
17 less medication than when they used to come to the  
18 hospital to get the injections.

19 We're not exactly sure why that is, but when  
20 the patients report back to us, they tell us that  
21 it gives them great confidence to have that  
22 control, to have that drug with them. And as you

1 can easily imagine for patients with that disease,  
2 there's a lot of stress anticipating the next  
3 attack, when will it come, to the extent where some  
4 of them have anxiety disorders and are really  
5 having a hard time dealing with this.

6 This stress adds as a trigger to the  
7 severity and the activity of the disease. So  
8 knowing that they have something that allows them  
9 to control an attack, actually in many patients  
10 reduces the activity of the disease, and they don't  
11 need that much medication anymore.

12 So taking these three years of experience  
13 together, it works just as well if not better when  
14 the patients use it, and the safety profile is  
15 actually better when they use it than when the  
16 doctor gives it to them.

17 MR. MULLINS: And therein lies my question.  
18 If there's so much efficacy in self-administration,  
19 why is there such a disparity between self-  
20 administration and onsite injection? It seems that  
21 since there is such, as you state, a greater  
22 confidence amongst the patient population and

1 greater usage that leads to a regression of  
2 symptoms, why is there such a disparity between  
3 self-administration and onsite application of the  
4 therapy.

5 DR. MAURER: I'm not sure where --

6 DR. CAMMARATA: Could you clarify your  
7 question, please?

8 MR. MULLINS: Yes. I'm just trying to  
9 understand why isn't there greater numbers as far  
10 as self-administration in the EU versus onsite  
11 injection by a medical staff person.

12 DR. KRISHNAN: So I'm going to -- I think  
13 we'll have the sponsor perhaps answer that one  
14 single question, and then what I'd like to suggest  
15 is we move on to the voting questions. There is an  
16 entire opportunity to discuss the self-  
17 administration again. We're going to get behind if  
18 we get too much further down on this single point.

19 So does the sponsor want to address  
20 Mr. Mullins as best as it can at this point?  
21 You'll have another opportunity.

22 DR. CAMMARATA: Your question is about the

1 number of patients using self-admin; is that --

2 MR. MULLINS: Exactly.

3 DR. CAMMARATA: Well, actually, in Europe,  
4 it has just been approved, so the launches are just  
5 starting now. So I believe, as Dr. Maurer has  
6 stated, he's just started switching his patients  
7 over to using icatibant on-demand. So it's because  
8 it wasn't available officially as self-  
9 administration in Europe until -- I believe it was  
10 March or April of this year. So it's only just  
11 been approved.

12 DR. KRISHNAN: Okay. Well, thank you very  
13 much.

14 I'm going to suggest we move to the question  
15 number 2, and let me just read that. For the  
16 voting question number 2, we will be using the  
17 electronic voting system. Each of you has three  
18 voting buttons on your microphone labeled yes, no  
19 and abstain. Once we begin the vote, please press  
20 the button that corresponds to your vote.

21 After everyone has completed their vote, the  
22 vote will be locked in. The vote will then get

1 displayed on the screen. I will read the vote from  
2 the screen into the record. Next, we will go  
3 around the room and each individual who has voted  
4 will state their name and vote into the record as  
5 well as the reason why they voted as they did.

6 So let me suggest that we've had a  
7 considerable amount of discussion I think on  
8 several of the points. I think we're ready to  
9 begin the voting section. Let me just read the  
10 question again, question number 2, which is -- it's  
11 interesting. The wording I have here and what's on  
12 the screen is slightly different. So let me read  
13 the one on the screen so I don't confuse people.

14 I guess it should say, do the data provide  
15 substantial and convincing evidence of a clinically  
16 meaningful benefit for icatibant in the treatment  
17 of acute attacks of hereditary angioedema? So  
18 you'll need to vote on that, and then I think when  
19 you provide the rationale, you're welcome to add;  
20 if not, then what further data should be obtained.

21 Kristine, are there any other comments you  
22 want to make, or do we go ahead and press our

1 buttons to vote?

2 DR. KHUC: If they're ready to vote.

3 DR. KRISHNAN: Okay. Why don't you go ahead  
4 and vote, please?

5 [Vote taken.]

6 DR. KRISHNAN: After I voted, it's still  
7 blinking. Is it supposed to keep blinking?

8 Okay. So if it keeps blinking, I guess  
9 you're okay.

10 If everyone can just revote, hopefully, the  
11 same vote, that way we'll --

12 [Laughter.]

13 DR. KRISHNAN: So I'll read out that there  
14 were 12 votes yes, 1 vote no, zero abstain.

15 We will now begin by going around the room,  
16 and if each of you can then state your name and the  
17 vote for the record as well as the reason why you  
18 voted that way. I'm going to begin to my right  
19 with Dr. Borish.

20 DR. BORISH: I'll keep it short. The data  
21 showing efficacy were robust, and I voted yes.

22 DR. STONE: Kelly Stone. So I think the

1 data presented is convincing showing a clinically  
2 meaningful benefit.

3 DR. PLATTS-MILLS: Dr. Platts-Mills. I  
4 voted yes. Given the remarkable variability of the  
5 disease and its prevalence, the data provides  
6 convincing evidence for efficacy and safety.

7 DR. SHEPHERD: Gillian Shepherd, I voted yes  
8 because I think that consistently the effect of the  
9 drug was approximately two hours, and although  
10 there may be debate about the placebo and the time  
11 interval between the drug's effect and the various  
12 interventions, consistently, the drug effect was  
13 robust.

14 DR. GREENBERGER: Paul Greenberger. I voted  
15 yes. I believe the data as shown by the composite  
16 of VAS-3 in FAST-3 definitely show a convincing  
17 effect, and I said yes.

18 DR. TRACY: Jim Tracy. I voted yes. I  
19 think that the data are quite compelling. There's  
20 a little confusion with the VAS and the VAS-3 as  
21 well as the placebo. All those were addressed  
22 satisfactorily in our discussion.

1 DR. POSNER: Phil Posner. I voted yes. I  
2 felt the data was really good as far as the  
3 physiological effect, the pharmacological effect  
4 and also the psychological effect. And something  
5 that hadn't been mentioned is that everyone has  
6 agreed that the earlier the drug is given, the  
7 greater the effect and the better the treatment.  
8 And, clearly, self-administration of this  
9 particular drug gives it an early administration  
10 rather than having to go through emergency rooms.  
11 So I think it's clearly effective on all points.

12 DR. MAUGER: I voted yes. I thought the  
13 preponderance of the evidence was strong. I have  
14 reservations, which I expressed earlier, and I'll  
15 spare the audience listening to that again.

16 [Laughter.]

17 DR. KRISHNAN: This is Jerry Krishnan, and I  
18 voted yes. I thought the evidence was consistent  
19 and compelling.

20 MR. MULLINS: I'm Rodney Mullins. I voted  
21 no, and I did so because of the -- obviously, there  
22 were indications that the drug was -- the therapy

1 was effective in the cases studied. My issue is  
2 what I mentioned earlier, making generalized  
3 statements from this slice of the population from a  
4 public health standpoint, that there were many  
5 populations, subgroupings such as women, such as  
6 men, that were under-represented.

7 So that was my issue of making this all-  
8 encompassing statement about the population that  
9 might not reflect the entire public. Thank you.

10 DR. PORTNOY: Jay Portnoy. I voted yes. I  
11 was convinced that the endpoint was a valid way of  
12 measuring the response. I saw a clear difference  
13 that was not only statistically significant but  
14 also, to me, appeared to be clinically important,  
15 and that's important to differentiate between the  
16 two. And because of all of those, I felt that this  
17 drug did show evidence of efficacy.

18 DR. JACOBY: David Jacoby. I voted yes. To  
19 me, the two issues with the data, one being the  
20 lack of effect in FAST-1 related to the shorter  
21 duration to resolution of the placebo group and the  
22 other being any potential issues of unblinding,

1 were both adequately addressed, the first by the  
2 timing of administration of the drug in placebo,  
3 the second by I thought an effective presentation  
4 of subgroup analysis.

5 DR. FOGGS: Michael Foggs. I voted yes. I  
6 was impressed with the data, especially as it  
7 relates to the leading cause of death for those who  
8 succumb to HAE, which is laryngeal attacks. And I  
9 think the time to onset of initial symptom  
10 improvement was impressive.

11 DR. KRISHNAN: Well, thank you very much. I  
12 think we probably still have some time to go to  
13 voting question number 3, and then we'll take a  
14 break. So let me have question number 3 put up on  
15 the screen, please, and I'll read it out loud from  
16 the screen.

17 Has the safety of icatibant been adequately  
18 assessed for the treatment of acute attacks of  
19 hereditary angioedema? If not, what further data  
20 should be obtained? So please vote yes, no or  
21 abstain, and then we'll repeat the exercise we just  
22 went through.

1 [Vote taken.]

2 DR. KRISHNAN: So I'll read out that there  
3 were 11 votes yes, 1 no, and one abstain. Let me  
4 now begin from the opposite side of the room. I  
5 was instructed to be fair and balanced during this  
6 meeting. So, Dr. Foggs, we'll start with you.

7 DR. FOGGS: I voted yes. I think the fact  
8 that there were no deaths, no episodes of  
9 anaphylaxis, and no withdrawals was sufficiently  
10 convincing for me to vote yes.

11 DR. JACOBY: David Jacoby. I voted yes. I  
12 think that the lack of serious adverse effects,  
13 and, to me, the lack of any evidence that this was  
14 actually causing exacerbations of the HAE were  
15 convincing.

16 DR. PORTNOY: I'm Jay Portnoy. I also voted  
17 yes. To me, the adverse events in the drug were  
18 comparable if even less than in the placebo group,  
19 and that convinces me that it's a relatively safe  
20 product. The only reservation about that is the  
21 skin test or the skin reactions, which aren't  
22 considered to be adverse events. We're used to

1       treating those with allergy shot reactions anyway,  
2       so that doesn't seem like a serious concern. And I  
3       think the consequences of not treating is much  
4       worse than any adverse events that the patient may  
5       have experienced.

6               MR. MULLINS: Rodney Mullins, a couple of my  
7       concerns were the fact that the second severe  
8       adverse effect was a recurrence of HAE. That was  
9       the second most prominent SAE that concerned me.  
10      The other issue was I didn't have enough  
11      information on the relevance and the interaction of  
12      this particular issue, this particular -- with HAE,  
13      where patients that had cardiovascular disease,  
14      obesity, other comorbidities. I wanted to  
15      understand that more, but I didn't have enough  
16      information to make that decision because I think  
17      this population, because they're immobile, because  
18      they struggle with other issues, I think there's  
19      some exposure there that I wasn't comfortable with  
20      making a decision on safety.

21              DR. KRISHNAN: I'm Jerry Krishnan. I  
22      thought that the data that were presented made me

1 feel comfortable that the safety was adequately  
2 evaluated in the study population.

3 I do, though, want to recommend to the FDA  
4 that a registry be entertained because I think that  
5 we know very little about how this might look like  
6 once it's put out in the real world, and I think  
7 it'll help move the field forward if we actually  
8 created a uniform registry to identify who all  
9 received this medicine once it gets out.  
10 Certainly, our patient demographics in this country  
11 may not necessarily reflect in the entire study  
12 population to date.

13 DR. MAUGER: Dave Mauger. I voted yes for  
14 the reasons articulated by the other members of the  
15 committee so far.

16 DR. POSNER: Phil Posner, I abstained  
17 basically because I felt they proved it was safe  
18 within a very limited population that they  
19 presented, and I would really like to see the  
20 registry carried out in a larger group that will  
21 include pregnant women, minorities, and people with  
22 ischemic disease such as Raynaud's, as well as a

1 coronary ischemic disease, which everybody else  
2 talked about. And so I think what they presented  
3 is fine, but the registry will answer those  
4 questions as it goes on for longer periods.

5 DR. TRACY: Jim Tracy. I, too, voted yes.  
6 I think in the near term, as mentioned, no  
7 anaphylaxis, no deaths, no withdrawals. I do,  
8 however -- as I reflected on this, I could have  
9 abstained also. I have concerns about the  
10 reproductive issues that have been present in the  
11 animal studies. I think the registry will address,  
12 hopefully, some of those items.

13 DR. GREENBERGER: Paul Greenberger. I voted  
14 yes. I thought the safety had been adequately  
15 assessed. Suggestions, as some others have said,  
16 comorbidities, although I would think that the  
17 patient with multiple comorbidities might be at  
18 more risk of not receiving treatment with this drug  
19 than receiving it.

20 DR. SHEPHERD: Gillian Shepherd. I voted  
21 yes. I think the safety was more than adequately  
22 investigated in this study. I think it was very

1 thorough, and I think it's actually remarkable  
2 that, compared to other agents that are available,  
3 practically nothing of significance was  
4 demonstrated. I note the pregnancy is an exclusion  
5 for this study. You'll never be able to answer  
6 that question. But I do support a registry for the  
7 primary reason of collecting information on  
8 patients to help further studies going forward have  
9 a patient population buy-in and anecdotally gather  
10 this sort of information that is just impossible to  
11 get in a clinical trial.

12 DR. PLATTS-MILLS: Tom Platts-Mills. I  
13 voted yes. I think there were two issues that I  
14 was concerned with; that is, were there any  
15 evidence of an exacerbation of the disease? Are  
16 there any patients in which this agent would act in  
17 the way that fresh frozen plasma can? And there's  
18 no evidence to date, but, clearly, that's something  
19 that should be followed long-term. And no  
20 evidence -- the other possibility was that it might  
21 paradoxically act as an agonist under certain  
22 circumstances, and there doesn't seem to be any

1 evidence, that we've seen, that says that, so I  
2 voted yes.

3 DR. STONE: Kelly Stone. I voted yes. I  
4 was reassured by the data presented in the trials  
5 as well as with the postmarketing data that was  
6 discussed in the packet.

7 DR. BORISH: Larry Borish. I voted yes. I  
8 second everything Dr. Platts-Mills and  
9 Dr. Greenberger said, and I'll add to  
10 Dr. Greenberger's comment. It's kind of  
11 interesting that the only ischemic complication in  
12 this study occurred in the placebo group.

13 DR. KRISHNAN: Great. Thank you very much.

14 I think what we can do is why don't we take  
15 an early break. We'll take a 15-minute break and  
16 reconvene at 3:10. Panel members, please remember  
17 that there should be no discussion of the issue at  
18 hand during the break amongst yourselves or with  
19 any members of the audience. Thank you.

20 (Whereupon, a recess was taken.)

21 DR. KRISHNAN: So we're going to go ahead  
22 and get started, if you want to take your seats,

1 please. We have one more voting question and one  
2 discussion turning into a voting question.

3 [Pause.]

4 DR. KRISHNAN: So I think we're going to go  
5 ahead and get started. The issue at hand  
6 is -- let's see here. So question number 4, if I  
7 could have question number 4 put up on the screen.

8 So question number 4 is do the efficacy and  
9 safety data provide substantial evidence to support  
10 approval of icatibant for the treatment of acute  
11 attacks of hereditary angioedema in patients  
12 18 years of age and older? And if not, what  
13 further data should be obtained?

14 Please go ahead and vote on your microphone  
15 as yes, no, and abstain, and then we will go  
16 through the discussion parts of how you voted.

17 [Vote taken.]

18 DR. KRISHNAN: So the voting results are  
19 12 yes, 1 no, zero abstain. And as we did before,  
20 we will go around the room, and this time begin  
21 back again with Dr. Borish, if you could state your  
22 name, how you voted and some rationale.

1 DR. BORISH: Larry Borish. We were  
2 instructed to keep our votes consistent, and I  
3 voted yes for Question 2 and 3.

4 [Laughter.]

5 DR. STONE: Kelly Stone. I voted yes. Both  
6 efficacy and safety were demonstrated.

7 DR. PLATTS-MILLS: Tom Platts-Mills. I  
8 voted yes for the reasons that I gave for the two  
9 previous questions.

10 DR. SHEPHERD: Gillian Shepherd. I voted  
11 yes for exactly the same reasons.

12 DR. GREENBERGER: Paul Greenberger. I voted  
13 yes for the same reasons, and just add this is a  
14 very serious potentially fatal disease that has a  
15 quick action treatment proposed to us.

16 DR. TRACY: Jim Tracy. I voted yes for the  
17 reasons previously stated.

18 DR. POSNER: Phil Posner. I voted yes, and  
19 the key word was "substantial evidence." And I  
20 think the evidence was substantial. I'm still a  
21 little worried about the teratology, and I think  
22 there needs to be a warning that the teratology

1 research hasn't been done to the extent that it  
2 might be done.

3 DR. MAUGER: David Mauger. I voted yes for  
4 the reasons before.

5 DR. KRISHNAN: Jerry Krishnan. I voted yes,  
6 and I'll make a call once again for a registry.

7 MR. MULLINS: Rodney Mullins. In the name  
8 of consistency, I had to vote no. I didn't want to  
9 look unstable.

10 [Laughter.]

11 MR. MULLINS: But to confirm my cognitive  
12 abilities, I'll just substantiate my response, and  
13 it was primarily based on the fact that I had  
14 concerns about the insufficient responses to the  
15 effect of the toxicity on women, in particular,  
16 pregnant women. I wasn't satisfied with that, in  
17 particular, because I work on several projects with  
18 infertile women, and that's a very sensitive issue  
19 right now with a large population within the U.S.  
20 and abroad. So that issue is big with me.

21 But there were other questions I had that  
22 were unanswered, so I just wanted to give you some

1 detail as to why that was a concern of mine because  
2 there was never any adjudication as to what  
3 happened, what was the issue with the aborted  
4 pregnancies. I never received a response to that.  
5 There was never any response to what happened to  
6 three of the women that had high levels of toxicity  
7 who had to drop out of the trial. So that was the  
8 rationale for my response. Thank you.

9 DR. PORTNOY: Jay Portnoy. I voted yes for  
10 the reasons I stated previously.

11 DR. JACOBY: David Jacoby. I voted yes. I  
12 was convinced by both.

13 DR. FOGGS: Mike Foggs. I voted yes for the  
14 reasons stated previously. I'd like to add that  
15 despite having voted yes, I'm concerned about the  
16 utility of this treatment unless it's made  
17 available, if so, being significant in the absence  
18 of self-administration.

19 DR. KRISHNAN: Okay. Well, thank you.

20 We'll move on then to the discussion  
21 question number 5. I'm told that the FDA has also  
22 created a voting question version of this. So no

1 need to ask for a voting question; we will have  
2 one. But we do want to have some discussion around  
3 the point of self-administration, and so I'd like  
4 the committee now to consider and discuss the  
5 potential impact of self-administration on the  
6 safety and efficacy of icatibant, if any.

7 One second, her pen is -- I'm waiting for  
8 Dr. Khuc to write the names here.

9 Dr. Shepherd.

10 DR. SHEPHERD: I think that the bottom line  
11 about self-administration is the fact that  
12 50 percent of affected patients will have an  
13 episode of laryngeal edema and 30 percent of those  
14 will die. And secondly that I wasn't aware, but  
15 the sponsor told us, that only 50 percent of the  
16 hospitals in the United States have emergency  
17 treatment for hereditary angioedema. I think the  
18 next question -- and that really is the bottom  
19 line.

20 The next question is, do the data support  
21 early administration? And I think the  
22 extrapolation of the previous data on the

1 C1 inhibitor and certainly the data that was  
2 presented to us today may not be definitive but  
3 certainly seem to support strongly early  
4 administration. I was intrigued by the fact that  
5 having the comfort factor of the ability to self-  
6 administer decreased stress and therefore perhaps  
7 decreased actual incidence.

8           The other big question, is there any  
9 downside to giving an injection? And from what we  
10 have seen, although not specifically addressed, I  
11 think we can extract from the data that we have  
12 seen so far, that there does not seem -- there are  
13 no safety issues that are apparent; therefore,  
14 there's no apparent downside to injecting the drug  
15 if the patient is not having an attack.

16           I think other issues of are the patients  
17 capable of doing the injection, I think that's  
18 practically moot. They may be afraid of it, but  
19 there are multiple disease models where patients  
20 self-inject. And I think that's abundantly clear  
21 that they're all perfectly capable.

22           I think that the other question that

1 sometimes seems to be raised, are these patients of  
2 capable of diagnosing themselves whether or not  
3 they're having an attack. I think any patient and  
4 any physician will tell you that absolutely they're  
5 capable. No one's going to mistake -- if you've  
6 treated these patients, not one of them is going to  
7 mistake an onset of an abdominal attack versus an  
8 acute abdomen for some other reason. And if they  
9 give themselves the injection, no downside; if it  
10 happens to be an acute abdomen, they're going to  
11 end up in the ER anyway.

12 So for all of those reasons, I very strongly  
13 support that this be voted or at least approved for  
14 self-administration.

15 DR. KRISHNAN: Great. Thank you very much.

16 Dr. Platts-Mills.

17 DR. PLATTS-MILLS: I would like to stress  
18 this issue that one of the real -- we are control  
19 freaks; that is, we really want patients to have  
20 control. That is, that the more you get patients  
21 to have control, the more they can feel they have  
22 control, and this is potentially a really big move

1 in terms of self-control by patients with HAE; that  
2 is, having an injection themselves really not only  
3 makes them able to move faster but have much less  
4 anxiety; because, as we know, going to an emergency  
5 room is an incredibly high anxiety event. I mean,  
6 you're playing Russian roulette with the physicians  
7 you meet in an emergency room. That's not a good  
8 idea. So being able to control it yourself is the  
9 major plus.

10 The other thing is that injection with a  
11 25-gauge needle sub-Q, patients get very good at  
12 indeed. The adrenaline auto injector by comparison  
13 is incredibly difficult to teach because you can't  
14 actually teach the injection. You can teach a  
15 25-gauge needle. I mean, I remember very well the  
16 old adrenaline syringes where we had a 25-gauge  
17 needle and you taught people how to inject with it,  
18 and they said oh, well, that doesn't hurt; I'm fine  
19 doing that. Those with the auto injectors are very  
20 unhappy and constantly anxious.

21 So the whole issue of decreasing anxiety so  
22 the patient can make rational decisions and has

1 control of themselves -- and the real benefit of  
2 this medicine that I see will be self-  
3 administration.

4 DR. KRISHNAN: Great. Thank you.

5 Let's see here. Dr. Mauger.

6 DR. MAUGER: I'm not a physician, so maybe  
7 I'll just pose this as a question for the treating  
8 physicians. It looks like 20 to 30 percent of  
9 participants in the open label may not respond to  
10 icanitibant, and I wonder whether this -- any  
11 possibility the patients would be overly confident,  
12 and it might delay the procedure to an emergency  
13 room when they should have gone immediately because  
14 they maybe were a little less concerned about it.

15 I'm certainly aware that these patients are  
16 very much self-aware of the dangerousness of the  
17 disease and these attacks, but I would just wonder  
18 whether there are other models for this in other  
19 diseases where this kind of access to treatment  
20 inadvertently causes delays in seeking medical  
21 care.

22 DR. KRISHNAN: So if I could take the

1 chair's prerogative on this, I just wanted to ask  
2 the sponsors for the EASSI study you were doing,  
3 and we have incomplete data on it because that  
4 study's not completed. But the protocol that was  
5 used in that study, were patients instructed to go  
6 to their healthcare provider after auto injecting,  
7 or were they told well, after you do this, you can  
8 stay home and then decide if things don't get  
9 better, then maybe you ought to go? How was that  
10 managed?

11 DR. CAMMARATA: In that protocol, in that  
12 study since that was the first study looking at  
13 self-injection, all the patients received the first  
14 syringe and did their dose at home. And then the  
15 next day, they would come in at some point and  
16 later on follow up. If they felt they needed  
17 another injection, they were asked to go back to  
18 see the physician to get that second injection.  
19 And there was only one or two patients out of that  
20 entire population of 56 that felt they needed  
21 another one.

22 DR. KRISHNAN: So the data that we have on

1 safety was designed in a way that patients could  
2 self-treat and then decide on their own whether  
3 they needed --

4 DR. CAMMARATA: Yes.

5 DR. KRISHNAN: -- seek additional medical  
6 attention?

7 DR. CAMMARATA: Yes. Now, we did instruct  
8 all laryngeal patients if -- and we would recommend  
9 that anybody with a laryngeal attack immediately  
10 seek medical care after self-dosing.

11 DR. KRISHNAN: So I would ask perhaps other  
12 members of our committee how that might weigh in on  
13 this given Dr. Mauger's question. I think that's  
14 an important question for me, too. At least in the  
15 asthma world, we worry quite a bit that people  
16 potentially self-medicate to an extreme and then  
17 perhaps seek attention late. And what do other  
18 members of the committee think about that potential  
19 risk?

20 Dr. Greenberger first.

21 DR. GREENBERGER: It's a different disease,  
22 but I take care and study a lot of people with

1 idiopathic anaphylaxis where there is also a threat  
2 to life. And the program, you often -- starts with  
3 intense abdominal pain as well, which patients  
4 recognize. And at that point, they're supposed to  
5 use their self-injectable epinephrine, which they  
6 often do, and that can help abort an attack or stop  
7 the progression. And, in fact, some of them do not  
8 go to the emergency room, and also, in that  
9 condition, doctors don't always know what  
10 idiopathic anaphylaxis is, either.

11 But I have not seen harm from the self-  
12 administration. In fact, I would -- and I'm hoping  
13 that the study that Dr. Maurer talked about is  
14 positive because we frankly haven't seen the data  
15 from the self-administration experience. So we're  
16 assuming that it will be consistent with what we  
17 think, but we haven't seen it yet.

18 DR. KRISHNAN: So I'm just going to go back  
19 down that list. Dr. Posner.

20 DR. POSNER: Everybody's already addressed  
21 everything really well. One suggestion I would  
22 make is they do a YouTube video on the injections.

1 They did it for the MS for the Avonex, and it's a  
2 very effective way of reaching the community.

3 DR. KRISHNAN: Dr. Tracy.

4 DR. TRACY: Well, I'll just go on the record  
5 that I support self-administration and everything  
6 that goes with it. Obviously, we're dealing in the  
7 study with a group of highly motivated individuals,  
8 and I think empowerment is important. I think a  
9 lot of times we reflect on our own patients that we  
10 care for day-to-day, and I have at least one  
11 patient that I would have to really take a couple  
12 big deep breaths before I sent her home on her own  
13 to do this, a lot of education. Just again  
14 addressing Dr. Maurer's point about how to do it,  
15 when to do it, but also when to seek further care.  
16 I think that's really an important consideration.

17 DR. KRISHNAN: I think I was listed next.  
18 So I think the concept of self-administration, it  
19 feels natural that this ought to be encouraged.  
20 And at least the data seems to be that there's some  
21 safety evidence to support that. But there is  
22 something awkward in my mind about voting on this

1 particular piece when we know there's additional  
2 data that perhaps will provide more clarity to  
3 address this question.

4 So I guess I would ask the sponsor, if I  
5 could, we have 56 patients' worth of data and those  
6 data are encouraging, to my mind, but how many  
7 total patients are enrolled and when we will  
8 actually have the final results of EASSI-3? It  
9 seems a little bit out of order, in my mind, to be  
10 voting on this, but I'd like to hear from you about  
11 when we would learn about the results of EASSI-3.  
12 I'm sorry. The EASSI study.

13 DR. CAMMARATA: Yes. That study, I believe  
14 the last patient was enrolled this week; is that  
15 correct? Yes.

16 So, yes. I believe it was just enrolled.  
17 So they'll be doing data cleanup and getting the  
18 data since the last patient finally had their  
19 attack, and it should be later this summer to have  
20 the information.

21 DR. KRISHNAN: So this summer, the idea is  
22 that you'll have the final results; is that right?

1 DR. CAMMARATA: Yes.

2 DR. KRISHNAN: And what is the process at  
3 this point for communicating those results to the  
4 FDA? Is that a planned event, or do you have a  
5 timeline for that?

6 DR. CAMMARATA: I don't have a final  
7 timeline for that. All information for all  
8 clinical studies would be submitted to all  
9 regulatory agencies, including the FDA.

10 DR. KRISHNAN: So if I could just follow  
11 that up for a moment to the FDA. And I'm sorry.  
12 You said the data will be available in how many  
13 months?

14 DR. CAMMARATA: Well, we'll be  
15 submitting -- it should be available later on this  
16 summer. We'll be submitting at the 120 days safety  
17 update.

18 DR. KRISHNAN: So we're at June, so I'm  
19 assuming sometime probably --

20 DR. CAMMARATA: There may be -- is there  
21 going to be a -- let me ask.

22 Will there be a data cut coming up for the

1 next -- yes? Okay. I just need somebody to say  
2 yes.

3 So, yes. They did a recent data cut. The  
4 final study report will be later on this year. So  
5 there will be something in the next few weeks going  
6 to the FDA.

7 DR. KRISHNAN: Okay. So the reason I want  
8 to ask that is, again, I think I've brought this up  
9 in different ways before, is that I don't quite  
10 know how to frame this in the ideal way. But we  
11 have, I think, comforting information from a  
12 limited number of patients. We'll have more  
13 definitive information at least from that study, it  
14 sounds to me in the short-term, a few months  
15 perhaps.

16 Is there an opportunity for the FDA to  
17 review again, once you have the full dataset  
18 or -- I'm just asking for some guidance from the  
19 FDA on how to deal with this unusual circumstance  
20 when a known study will be more mature and reported  
21 in not too long a time from now.

22 DR. ROSEBRAUGH: So I'm going to turn it

1 back on you-all, and I am going to mention just  
2 that age has robbed me of my short-term memory, but  
3 I do have a vague recollection that people wanted  
4 to vote on this.

5 [Laughter.]

6 DR. ROSEBRAUGH: So beware of what you ask  
7 for.

8 No. The way I would look at this is there's  
9 really no way we're going to get the study reviewed  
10 before approval. So if people really do think that  
11 it's important that at approval that this drug  
12 should be self-injected, they should vote that way  
13 because this study will not get reviewed before the  
14 PDUFA day. We're just not going to have time to do  
15 it.

16 So it's not that unusual where we really  
17 don't have data or we know there's another study  
18 coming in or something like that. So I think since  
19 you-all have made it an issue about voting on it, I  
20 think it is important to vote. And you can  
21 synthesize what you have now and think if that's  
22 enough for them to self-administer at approval.

1 DR. KRISHNAN: And just to follow up again,  
2 I'm sorry to perseverate on this point, but if the  
3 discussion was in favor and you will be getting  
4 additional data in some short time, I'm assuming  
5 there is a mechanism in place to re-review at that  
6 point, from your standpoint, whether the decision  
7 we're making today is supported by the additional  
8 data you will have in a few months.

9 DR. ROSEBRAUGH: Yes, it would come back in.  
10 Let me just kind of back up. If the decision -- if  
11 we decided to not approve it with self-  
12 administration, and they had a study that came in,  
13 they would send it in as a labeling supplement and  
14 ask us if we now thought there was enough data for  
15 self-administration.

16 If, on the other hand, we did approve it,  
17 and we approved it for self-administration, and  
18 something came in that showed us there's a safety  
19 risk, we would certainly go back and reevaluate  
20 that decision and see if it was in error and we  
21 needed to modify it.

22 DR. KRISHNAN: Please go ahead, yes.

1 DR. CAMMARATA: This is Sue Cammarata. I  
2 just also wanted to make one other comment. I'm  
3 not sure if you're looking at the adverse events or  
4 the serious adverse events, but I do want to remind  
5 you that for every trial, including this trial,  
6 anything that's seen as a serious adverse event has  
7 already been forwarded to the FDA. So, really,  
8 what we're seeing in the trial currently is just  
9 everyday adverse events with no special reporting.  
10 And every study we've had, the profile for  
11 icanitibant has been very similar. So I think that,  
12 as I said, serious adverse events are already going  
13 into the FDA on a regular basis.

14 DR. KRISHNAN: Great. Thank you.

15 Head back down the list. I think  
16 Dr. Strahlman, you're next.

17 DR. STRAHLMAN: I wanted to go back to the  
18 question that was raised earlier about the  
19 potential for if the product is made available for  
20 self-injection, that patients might not seek care  
21 or there might not be an effect. And I wondered if  
22 the sponsors could clarify also from the clinical

1 trial and also from the in-market use, if they're  
2 seen any tachyphylaxis in patients.

3 In other words, for patients who have  
4 repeated attacks, if the attacks -- has that worn  
5 off because I think that might inform our view on  
6 that.

7 DR. KRISHNAN: Does the sponsor have a  
8 comment? You might want to just get a chair up  
9 here.

10 [Laughter.]

11 DR. CAMMARATA: Get a little sofa chair  
12 here, get comfortable.

13 Sue Cammarata from Shire. Actually, what I  
14 heard in the request was looking at repeat data  
15 over the repeat attacks because we did have many  
16 patients who had repeat attacks, as I mentioned  
17 earlier. We looked at attacks. The most robust  
18 database we had was within the first five attacks  
19 because we have a number of patients that did that.

20 So let me just show you this first slide,  
21 and it gets a little bit -- slide up, please. And  
22 in this cut, we've done all the patients who

1 had -- all of them had five attacks at least. Some  
2 of them had more, because, as you recall, patients  
3 are coming in for repeat attacks. So as you go out  
4 to the 10th attack or the 15th attack, the number  
5 of patients gets smaller. But we felt that it was  
6 one way to say for those patients who have five  
7 attacks, what does their time to onset of symptom  
8 relief look like?

9           So in this slide, we have all the patients  
10 who have five attacks. So in the first over -- I  
11 have right-left dyslexia. On the left-hand side,  
12 the pink bar, are all the patients that had one  
13 attack. Then under the two, the two attacks, those  
14 are all the patients who had two attacks. The next  
15 are all the patients who had three attacks. So  
16 that's a first attack, second attack and third  
17 attack. And over here on the right-hand side are  
18 all the patients with five attacks, their first  
19 attack, their second attack, third attack, fourth  
20 attack, fifth attack. And you see consistently  
21 across the board, all the patients have the same  
22 time to onset of symptom relief, around two hours.

1           We also have done other analyses where we've  
2 looked at people who've gone beyond the five  
3 attacks. So we have patients, for example, with 10  
4 or 20 attacks. And, again, the numbers get  
5 smaller, but we see similar results where the  
6 results are similar with that time of onset around  
7 two hours consistently.

8           DR. STRAHLMAN: So those are medians, and so  
9 what do you have -- so what's the outside limit of  
10 potential harm here? Were there any patients who  
11 didn't respond after one or two?

12           DR. CAMMARATA: I think all the patients,  
13 even placebo patients, often don't have a response;  
14 it can be quite prolonged, and patients do use  
15 rescue medications.

16           Here is the slide for patient --

17           DR. POSNER: Do you have end values for  
18 those?

19           DR. CAMMARATA: I don't remember. No, I'm  
20 sorry. I don't think we've put the end value for  
21 the bars.

22           DR. POSNER: So there's a median of two

1 patients or --

2 DR. CAMMARATA: No, no.

3 DR. KRISHNAN: I'm sorry. Can both  
4 committee members and sponsor, if we could use the  
5 microphones, please?

6 DR. AMATO: David Amato, biometrics. I  
7 believe attack 5, there were 48 patients, and as  
8 you go to the left on this chart, there's obviously  
9 more. Attack 1 I think was around 225 attacks.

10 DR. CAMMARATA: Can you show me the  
11 composite VAS slide? And here's a slide. Now,  
12 this is portrayed in a different way where we  
13 looked at the composite VAS over time.

14 Slide up, please. This is for all patients  
15 who had multiple attacks over time. This is a  
16 composite VAS pooled, and this is attacks 1 through  
17 10. So you can see they sort of overlie each  
18 other, and then from next slide up, these are now  
19 the patients. The numbers are getting quite small  
20 now as you get to 20 attacks, but here's attacks 11  
21 through 20.

22 So, again, with small numbers, but I think

1 you can see there's a very consistent response in  
2 patients with icatibant even with up to 20 attacks.

3 DR. KRISHNAN: Okay. Thank you.

4 Dr. Greenberger, I believe you're next.

5 Okay. Dr. Portnoy.

6 DR. PORTNOY: Great. Thanks. I think this  
7 really is a safety issue, but it's not safety with  
8 the drug. It's safety with not making it available  
9 for self-injection by the patients. So we would  
10 never tell our patients who have anaphylaxis to go  
11 to the emergency room to get their epinephrine.

12 Why would we tell people with angioedema that they  
13 have to go to a medical facility to get their  
14 treatment for their acute angioedema attacks? That  
15 just makes no sense. It's not safe to do that.

16 What we have to consider when we're thinking  
17 about adverse events is whether the adverse effect  
18 of the drug is worse than the adverse effect of the  
19 disease being treated, and the disease kills  
20 people. So unless the drug has that kind of  
21 adverse effect, we need to make sure that it's  
22 available to our patients.

1           As Dr. Shepherd pointed out, half the  
2 hospitals in this country don't have the treatment  
3 to treat angioedema episodes in patients who have  
4 them, and I know that most of the hospitals that  
5 don't won't administer the patient's own drug when  
6 they bring it in.

7           I had one emergency room doctor who called  
8 me up and screamed at me because one of my patients  
9 brought their drug in to his emergency room and he  
10 refused to deliver it. He insisted on transferring  
11 the patient over to our hospital where we would  
12 deliver it.

13           So this is a major safety issue for our  
14 patients. This drug has to be made available for  
15 self-injection just like epinephrine, which, by the  
16 way, epinephrine has more side effects than this  
17 drug apparently has, and we give that all of the  
18 time. We train our patients to do that.

19           It's absolutely essential that it be made  
20 available for self-injection. And my suspicion is  
21 if it's not made available for that, we're all  
22 going to use it off label and do it that way

1 anyway. I personally intend it do it that way.

2 Thank you.

3 [Laughter.]

4 DR. PORTNOY: I'm going to do it off label  
5 if it's not approved for self-injection. That's  
6 legal, by the way.

7 [Laughter.]

8 DR. KRISHNAN: I think that's in the record,  
9 too, now. Okay.

10 [Laughter.]

11 DR. KRISHNAN: Let me go to Mr. Mullins  
12 quickly.

13 MR. MULLINS: My concern is just that  
14 sometimes in these settings we make assumptions  
15 about the public that everyone's the same as far as  
16 their accessibility to public healthcare. And so  
17 all I would admonish you is to tell you that  
18 obviously, within the setting of a clinical trial,  
19 there might not be any incident. But when you put  
20 this in the context of public health, the model can  
21 change, and I think we have evidence of the model  
22 changing because of accessibility issues, avoiding

1 follow-up care because of economics.

2 So I think there are variables that we're  
3 not considering because we are in this utopia of a  
4 clinical trial where there is intense support where  
5 there are physicians that are there waiting on you,  
6 but that doesn't always exist across the board.

7 So I think that without -- my primary  
8 premise is that, obviously, we're making this  
9 decision in isolation without a vast amount of  
10 information on how this will behave in the public  
11 setting. The public setting is not the clinical  
12 trial setting because people are making decisions  
13 on healthcare based on a number of different  
14 reasons, and oftentimes they're related to things  
15 that you might not have to worry about. So that's  
16 what I wanted to mention. Thank you.

17 DR. KRISHNAN: Great. Thank you.

18 Dr. Foggs.

19 DR. FOGGS: If we look at a host of chronic  
20 diseases, one of the cornerstones for facilitations  
21 of self-efficacy is always patient education, so  
22 that any new product that comes to market that is

1 FDA-approved should be coupled with intensive  
2 patient education to decrease the likelihood of  
3 abuse of medications or inadequate health-seeking  
4 behavior and risk-taking behavior. And so when we  
5 have a disease, whereby the worst-case scenario is  
6 death, I think that patient education will go a  
7 long ways to shift the locus of control to one that  
8 is internal based upon the patient's fundamental  
9 understanding of the disease, which will dictate  
10 how they use the product.

11 DR. KRISHNAN: Thank you.

12 Dr. Platts-Mills.

13 DR. PLATTS-MILLS: Yes. I just wanted to  
14 address the issue of the self-administration of  
15 other drugs and the history of what's happened. I  
16 mean, just thinking of nebulized albuterol, which  
17 was a hospital drug originally; insulin where when  
18 I was trained, the house surgeons, house  
19 physicians, had to work out the dose and get the  
20 blood sugars and give the injections. And then we  
21 suddenly realized that if you gave it to the  
22 patients and gave themselves -- blood sugar control

1 was much better. And patients now today, there's  
2 no one who would doubt that patients control their  
3 blood sugars better at home with education and  
4 self-administration. Adrenaline, which we've heard  
5 from several people.

6 But we use lots of other things, nebulized  
7 cromolyn and lidocaine for VCD at home, home use,  
8 and lots and lots of things. And in almost every  
9 case, when you really get to self-administration,  
10 management improved. Nitroglycerin.

11 [Laughter.]

12 DR. KRISHNAN: Dr. Stone.

13 DR. STONE: I guess my only comment is that  
14 it really should be in the armamentarium. And in  
15 terms of the risk-benefit, it's really up to the  
16 individual providers to assess for individual  
17 patients and safety in that setting.

18 DR. KRISHNAN: I think, Dr. Borish, you're  
19 next.

20 DR. BORISH: The best argument against it  
21 was Dr. Maurer's, and I wanted to comment on it.  
22 And that was the danger of delaying treatment by

1 home administration. Most of what we heard about,  
2 of course, is pain and angioedema. That is a  
3 morbidity but not life-threatening, clearly, and we  
4 have lots of testimony, both written and from the  
5 audience today, about how they overwhelming would  
6 prefer to be able to self-treat even if it  
7 potentially means they get to delay the wonderful  
8 care they get from the emergency room.

9 [Laughter.]

10 DR. BORISH: But the potentially dangerous  
11 thing is laryngeal edema and delaying that. Am I  
12 allowed to request slides? C-58?

13 [Laughter.]

14 DR. BORISH: Because this is actually very  
15 reassuring, because I think you could figure out 20  
16 to 30 percent nonresponders. There are two really  
17 nice things up here. One is that in the case of  
18 laryngeal edema, granted the numbers are low,  
19 95 percent are responders, and unlike pain and  
20 swelling where it's 2.2 hours, that's pretty fast.  
21 This drug works really well for laryngeal edema,  
22 and I don't think 36 minutes is an unreasonable

1 delay.

2 DR. KRISHNAN: Great. We worked our way  
3 through our list. I don't see anybody else listed.

4 Did any other committee members have  
5 additional comments about self-administration?

6 [No response.]

7 DR. KRISHNAN: Okay. So I think we've had  
8 our discussion, which seems to me there's  
9 substantial amount of interest in making available  
10 through self-administration because of reducing  
11 delays to care and perhaps even getting over  
12 problems with differences in access to care if the  
13 patients themselves can self-medicate. But there  
14 are concerns being discussed about perhaps if you  
15 take it outside of the study setting, that it may  
16 not behave in the same way. So those are the  
17 issues I think generally are discussed.

18 So let me move then to suggest we should go  
19 to the voting question related to this. So let me  
20 read it out loud. Do the data support the self-  
21 administration of icanitabant? And then as in other  
22 questions we looked at, if not, what further data

1 should be obtained?

2 Please go ahead and use your microphone  
3 voting, and then we'll go through the procedure we  
4 did for the other questions.

5 [Vote taken.]

6 DR. KRISHNAN: So the voting results are  
7 presented here. There were 11 yeses, 1 no, and  
8 1 abstention. And I think we're going to start to  
9 the left side again.

10 Dr. Foggs, if you could state your vote and  
11 then your rationale, please.

12 DR. FOGGS: My rationale for voting yes is  
13 because I think, number one, the administration is  
14 sufficiently safe to warrant allowing the patient  
15 to independently make a clinical decision about  
16 their disease about which they've been educated.

17 DR. JACOBY: David Jacoby. I voted yes. I  
18 considered abstaining, but I figured that I'm a  
19 critical care person and I'm used to dealing with  
20 uncertainty. I think that there's a lot of  
21 evidence that it's good to get this drug early, but  
22 I share what I took your concerns to be, that we're

1 making a decision excluding data that will shortly  
2 be available. And I would encourage the FDA to  
3 follow up on that data and reevaluate it. I think  
4 it's a little bit cavalier to say that this is not  
5 going to do any harm. And unless patients with  
6 this disease are selected to be a whole lot more  
7 self-aware than patients who have a chronic  
8 disease, I'm not sure that that generalization can  
9 be made.

10 DR. PORTNOY: Jay Portnoy. I voted yes. As  
11 I mentioned earlier, unless something really  
12 dramatic comes up like anaphylactic episodes in  
13 patients who are self-administering, I think that  
14 there's good evidence so far that would justify,  
15 plus the severity of the disease makes a compelling  
16 reason why patients need to be able to self-inject.  
17 Plus when I start prescribing it to my patients for  
18 self-injection, I'd like to do that on label.

19 Thank you.

20 [Laughter.]

21 MR. MULLINS: Rodney Mullins. I, too, would  
22 like to see the additional information that would

1       come from the study that was mentioned by the  
2       applicant to make a more informed decision.  And I  
3       think that I also would like to understand how  
4       self-administration would be handled by patients  
5       that have more severe cases, how they react to  
6       this.

7               I think there are a number of questions I  
8       have in my mind as it relates to self-medicating  
9       and how patients handle that, and would they handle  
10      that appropriately because we just have situations  
11      of addictions, improper administration.  So I want  
12      to see how -- I want to understand those  
13      complications so we know how to mitigate that.  
14      Thank you.

15              DR. KRISHNAN:  I'm Jerry Krishnan.  I voted  
16      yes because I think -- I struggled a little bit  
17      with the uncertainty because there are more data  
18      coming.  But I think part of my comfort in voting  
19      yes was that if there had been SAEs, it would have  
20      been reported.  And I think that plus the fact that  
21      the FDA's likely to obviously follow up on the  
22      results of that study give me some comfort that

1 with the available evidence, I think it should be  
2 approved to be self-administered.

3 DR. MAUGER: Dave Mauger. I abstained on  
4 technical grounds. This question was added under  
5 the argument the FDA should seek the input of  
6 treating physicians, and I'm not a treating  
7 physician.

8 DR. POSNER: Phil Posner. I voted yes.  
9 It's really a positive abstain. I think with the  
10 evidence we have, it should be self-administered.  
11 I'm a self-administrator, and I've been trained,  
12 and I know when I'm supposed and what I'm not  
13 supposed to do. And I think the individual  
14 physician knows their patient as to what's going to  
15 happen.

16 I take some of the caveats seriously because  
17 of financial issues. Some patients may not use it  
18 because they only have one left. But on the other  
19 hand, they may go to an emergency room that doesn't  
20 have it. And so I think it's important for the FDA  
21 to look at the additional data as it comes in. But  
22 right now, I think the preponderance of data is

1 it's important to have it available and then give  
2 the independence to the patient with the advice of  
3 their physician.

4 DR. TRACY: Jim Tracy again. I voted yes.  
5 I think, again, education is important. Patient by  
6 patient, I think on an individual basis, there may  
7 be individuals who are better suited to get it in  
8 the office versus at home. I think that the  
9 practitioner is in the best place to make that  
10 decision.

11 DR. GREENBERGER: Paul Greenberger. I voted  
12 yes. I would vote yes in capitals and urge the  
13 agency and the sponsor to expedite the whole  
14 process in what they can do to get this approved as  
15 well for self-injectable use. And secondly,  
16 regarding addictions, the people that get addicted  
17 are the ones who have not received products such as  
18 this because they're coming in, the pain is  
19 intense, they're getting dilaudid and opioids, and  
20 that can destroy their lives from addiction. So  
21 this is an advance that needs to be expedited.

22 DR. SHEPHERD: Gillian Shepherd. I voted

1       yes. I realize that the actual data are less than  
2       robust, but I think that the risk-benefit that  
3       everybody's elaborated is absolutely compelling  
4       that this should be self-administered.

5               DR. PLATTS-MILLS: Tom Platts-Mills, I voted  
6       yes really for the reasons that Dr. Tracy outlined  
7       so well. I think that physicians can perfectly  
8       well make this decision. There are clearly  
9       patients where it would not be a good idea, and  
10       there are patients in whom it's clearly immediately  
11       the correct idea. And the point that Jay Portnoy  
12       made, yes, it would be fun to be on label.

13               [Laughter.]

14               DR. STONE: Kelly Stone. I voted yes. I  
15       think it is important that it is available as an  
16       option for these patients, and the limited data  
17       that is presented already is certainly supportive.

18               DR. BORISH: Larry Borish. I voted yes  
19       because I trust the agency to ultimately make the  
20       right decision based on the data that will be given  
21       to them, but I really wanted you to get the sense  
22       of what this committee wanted to do, and I think

1 you heard it.

2 **Adjournment**

3 DR. KRISHNAN: Great. Well, thank you,  
4 everyone. I'd like to express my appreciation for  
5 everyone's assistance today, both the committee  
6 members, members of the audience, as well as the  
7 sponsor. I think we've had a good healthy  
8 discussion around the topic of approval regarding  
9 this drug, and the meeting is now adjourned.

10 DR. LIMB: Before everyone leaves, we just  
11 wanted to thank you for your feedback, and we  
12 appreciate all of the comments and consideration  
13 you put into the matter. Thank you.

14 (Whereupon, at 3:51 p.m., the meeting was  
15 adjourned.)

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