UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PATIENT-FOCUSED DRUG DEVELOPMENT FOR HEREDITARY ANGIOEDEMA

Silver Spring, Maryland

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P R O C E E D I N G S

(9:04 a.m.)

DR. LAPTEVA: Good morning and welcome to the public meeting on Patient-Focused Drug Development for Hereditary Angioedema. My name is Larissa Lapteva and I am the Associate Director in the Division of Clinical Evaluation, Pharmacology and Toxicology in the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research here at the FDA.

Today's meeting is the FDA's 24th meeting organized under the Patient-Focused Drug Development Initiative and as other meetings conducted in the past 5 years, it will center on patient's perspectives on the condition that we're discussing today: Hereditary Angioedema; it's symptoms, it's treatments, and the impact of this rare genetic disorder on the lives of people who have it.

I would like to thank everyone who is participating today, whether you're here in person or joining us online, thank you for your willingness to share your stories and your experiences with us. We have a very

packed agenda and without further ado, I would like to invite to the microphone, Donna Lipscomb, who is the Director of the Division of Manufacturers Assistance and Training here in the Office of Communications and CBER and she will facilitate our meeting today. Donna.

MS. LIPSCOMB: Thank you so much. I really am excited to be here. I'm so excited to meet each and every one of you. My role as Facilitator really is going to be, to make sure you have a chance to talk about your experiences and to make sure that what you want to know us to hear. That was a good sentence I like that. Whatever you want us to hear, we're going to make sure we have time.

So our agenda, just to go over really quickly; we have opening remarks, overview of the Patient-Focused Drug Development Program, we have the discussion topics that Larissa spoke about. There will also be open public comments, that's at the end of the meeting. And you have the ability to -- if you also wanted time to say something more prepared, you can sign up out at the

registration desk if you did not already. There's 30 minutes and the time will be based on how many people sign up. If there's 30 people everyone get's 1 minute. And then we'll have closing remarks, okay?

First off before we get started I want to introduce -- I want the FDA panel to be able to introduce themselves, so we'll start.

Dr. GOLDSMITH: Yes, hi. Jonathan Goldsmith. I'm from the Rare Diseases Program in the Office of New Drugs in the Center for Drugs and I'm glad to be here this morning. Welcome to you all.

MS. MALONEY: Good morning and welcome from me as well. I'm Diane Maloney. I'm the Associate Director for Policy in the Center for Biologics Evaluation and Research.

Dr. PUROHIT-SHETH: Good morning and welcome from me as well. I'm Tejashri Purohit-Sheth. I am the Division Director for Division of Clinical Evaluation, Pharmacology and Toxicology in the Office Tissues and Advanced

Therapies in CBER.

MS. CHALASANI: Good morning everyone. My name is Meghana Chalasani and I work in the Office of Strategic Programs in the Center for Drugs and Research and Evaluation.

MS. MUELLER: Good morning. I'm Christine Mueller from the Office of Orphan Product Development

DR. LAPTEVA: Larissa Lapteva and I've already introduced myself. Welcome everyone.

DR. MULLIN: Hi, I'm Theresa Mullin. I direct the Office of Strategic Programs in the FDA Center for Drugs. Good morning.

MS. LIPSCOMB: Thank you so much. I know that some of you were in line at the kiosk for lunch so at the first break, if you didn't get your lunch preordered, you can do it then and if you don't get it preordered you are welcome to go up and order a sandwich.

The restrooms are -- if you go out past the kiosk, make a right and down the hall, you'll see the restrooms there.

And I also want to make sure -- I welcome the people in the webcast. Throughout the process we will be giving polling questions for people. At the table you have a really cute little blue clicker that looks a lot -- if you were in Who Wants To Be A Millionaire where you get to click an answer, that's what we're going to ask you to use. And they're marked either one or A, click the associated number when you're giving an answer. But the real key is to make sure you see whatever you picked come right on the display, then it has to go away. So if it's a time where it says, pick up to three, pick as many as you want. If you don't let that go away and you keep clicking, it's only taking the first one so make sure you click it see the red, let it go away and we'll try to make sure we give you enough time to do that.

And I think now, I'd like to introduce Wilson Bryan.

DR. BRYAN: Good morning. My name's Wilson Bryan and I work in the Office of Tissues

and Advanced Therapies in the Center for Biologics here at the FDA.

On behalf of the FDA, I've been asked to make a few opening remarks. What I would like to talk about is education. My own medical education began approximately 40 years ago when I enrolled in medical school. And the opportunity to become a doctor was for me a great honor and privilege. In medical school I learned about many diseases. I don't remember whether I learned about Hereditary Angioedema in medical school or whether what I learned about HAE was lost among the many lessons about more common diseases.

I think we all know that rare diseases are too often forgotten, overlooked, and neglected. We are fortunate that the scientific community and pharmaceutical companies have developed several treatments for HAE, however we recognize that the available treatments have severe limitations, that they do not cure the disease and they have side effects. Today's meeting will serve to advance the development and

regulation of new and better treatments for Hereditary Angioedema.

Particularly what we learn at this meeting will help the FDA to think about how clinical trials should be designed, what endpoints are meaningful to patients, and how to balance benefits and risks when we're thinking about a new product. Which reminds me that while I may have many brilliant teachers in medical school, most of our education as physicians comes from our patients.

At the FDA patients educate us in many way, including when they participate in clinical trials, when they serve on advisory committees, and when they and their caregivers participate in meetings like this. So I would like to thank the good folks who organized this meeting and thank particularly the patients and caregivers those of you who are making the effort to participate in today's meeting. You are providing my FDA colleagues and me the opportunity and the privilege to continue our education by listening

to you. I'll stop there and turn the agenda back over to Donna Lipscomb.

MS. LIPSCOMB: Thank you. We're going to ask Dr. Theresa Mullin to come up. She's the director of office of strategic programs at CBER.

DR. MULLIN: Good morning. So I'm here on the Center for Drugs. I've worked on the negotiations to authorize the 5th round of the Prescription Drug User Fee Act in which FDA makes commitments to improve the programs and we also negotiate a level of funding from industry which really helps us to hire people and have enough staff to do the work that we do in various ways. And part of what we did -- and the reason I'm here today is as Larissa Lapteva mentioned this is the final meeting that we're having on patient focus so you're very special because, you know, a lot of people wanted to have meetings and we're like, no this is our last one for this authorization of the User Fee Program which ends actually next Saturday. The end of the authorization is the end of the fiscal year so this is the last meeting

that the FDA is running for this process and I want to tell you a little bit about why.

We, 5 years ago, realized that, as Wilson Bryan mentioned, we do have various ways of getting information from patients. One of the main ways we did that before we had this Patient-Focused Drug Development Initiative setup was to have individuals come in and become patient representatives and they might come to an advisory committee or they might just be part of a group that would weigh in. In order for a patient representative to do that, they have to clear for conflict of interest because they're weighing in on particular matters that have to do with a particular drug.

And that's a very important role to have patients play but the downside of it is, you can only have very few people do it. You have to go through a conflict of interest screening, so we hear from one person and the person that we're able to get a hold of and join that process may not even have the disease that's being discussed

in the condition for which the drug's being developed. So we needed a better way to get to the community of people who have a disease. So to hear from them directly because we understood that you have unique perspective, you really have the most critical perspective because the people with the disease can tell us best what it's like to live with the disease and any benefit that's going to come from a drug, they're going to experience any burden -- they're also going to be the one to experience it, so clearly that's a very important perspective for FDA to understand when we're trying to evaluate a drug and make benefit risk assessments.

So we needed this more systematic way to collect the information. So we had this meeting and we've been doing these meetings for 5 years, this is the 24th meeting that we're having like this. We committed to doing at least 20 but we found they're extremely helpful to FDA to better understand what patients are going through and really understand the burdens of the treatments we

have. So we understand that treatment burden and treatment disease burden both matter a whole lot.

So we've been doing these meetings and we're very much very looking forward from hearing from you today and hearing you perspective. It gives us an enormous amount of insight that we otherwise wouldn't get. We usually hear things that are not in the literature, or anywhere else, during these meetings and it's extremely helpful for us.

And this is just to quickly show you the wide range of diseases that we have covered in these meetings and, you know, today we're doing Hereditary Angioedema so this is something, I know, the doctors and the others staff here are really looking forward to hearing what you're going to tell us. And the way you're going to be asked about what it's like to live with your disease, what are the symptoms, what are the things that are most bothersome.

Then you're going to be asked about, you know, what you're doing to treat and how that's

going. With the clickers you'll be able to answer some of those questions and others. And then between what we hear in the room and the webcast and the docket -- that will stay open for a while so to have people submit any other information they may think of that would be relevant to these questions. We'll put all that together and analyze it and develop a voice of the Patient Report.

That's what follows each of these meetings, takes a couple of months, at least to get all that information together and carefully look at it and the transcripts from the meeting. And those reports have had extremely -- been a very valuable resource to FDA reviewers who go to look at those reports later. They use them to base discussions, we've heard companies go and look at those reports to understand what patients are going through and it helps to jumpstart their work and maybe developing patient reported outcome measures or looking at the performance characteristics of the drug they have in development. Patients have told us that these

reports are helpful to them because sometimes they never get to really hear what other people are going through, too and it's a chance to hear what other people are going through as well as their own experience.

And so it's served in a lot of different ways, and I will tell you that we've learned so much in these meetings, that we are proceeding to do a bunch of follow on work in this next authorization. So happily the User Fee Program got reauthorized so we're going to still be in business on October 1st and doing the Reviews of Drugs and Biologics but we're also going to be developing other follow on work to build on what we learning in these meetings.

And so I know we look forward to hearing what you're going to have to tell us today. And with that I'll turn it back to Donna. Thank you.

MS. LIPSCOMB: I am really excited to introduce Dr. Ross Pierce. He's a Medical Officer with Division of Clinical Evaluation, Pharmacology and Toxicology in OTAT. Ross.

DR. PIERCE: Good morning. So I'm in this sort of awkward position of giving background on a medical condition for which most of the people in this room are already very intimately familiar. So my talk's not going to be all encompassing so I'm sure there will be things that are important to you that I will not have an opportunity to touch on to during the discussion topics, particularly the first discussion topic on symptoms and impacts on your life, I'm very excited to have you amplify and fill in the gaps that will inevitably be there in my brief overview.

So Heredity Angioedema is a condition that involves recurrent attacks of a type of severe swelling called Angioedema that may involve various areas of the body including: the gastrointestinal tract, the arms, hands, legs, feet, face, tongue, throat, and/or voice box or larynx, and genitourinary system. The symptoms result in many, many hospitalizations and emergency room visits in the United States every

year and worldwide. And swelling of the larynx can be life threatening due to the risk of suffocation.

We can divide the areas of the body that are subject to acute HAE attacks into those involving the mucosa -- mucosal and non-mucosal attacks. So the mucosal attacks would include the rather common gastrointestinal tract attacks, which can show severe abdominal pain, nausea, and vomiting among the symptoms. The oropharynx, so the mouth and throat and larynx or voice box, where the mouth, tongue, throat swelling, hoarseness, and a type of noisy breathing called stridor, shortness of breath, and turning blue in the worse cases of laryngeal edema can manifest. Attacks of genitourinary tracts can involve lower abdominal pain and or genital swelling.

And then the non-mucosal attacks involve basically the skin and subcutaneous tissues of the limbs and the face for example.

So these attacks may involve just one of these locations or they can occur in more than one

location either at the same time or sequentially during the course of one attack.

These symptoms typically begin in childhood and worsen during puberty, but the onset of time is variable between patients. If untreated, attacks of swelling may occur on the average, perhaps 1 to 2 weeks, last perhaps 3 to 4 days without treatment, but this is highly variable between individuals in terms of attack frequency and how long each attack lasts.

The triggers for attacks include trauma, stress, infection, exertion, others and are often not identified at all.

So the prevalence of HAE has been thought, in the United States, to be between 1 and 10,000 to 50,000 individuals. It's estimated that there are perhaps 6,500 individuals in the U.S who have HAE. This is considered a rare disease. It's resulted in 30,000 emergency room visits per year in the United States.

It's inherited from one parent most typically. This is called Autosomal Dominant

Inheritance. But it can also occur from spontaneous changes or mutations in the genes responsible for the disorder.

We can divide HAE into three types, in terms of the mechanism. The first involves about 85% of the cases, so it's by far the most common. And here we see reduced levels in the blood of a protein called C1 Esterase-Inhibitor, which we abbreviate C1-INH.

Type two which comprises about 15% of cases, the blood levels of C1-INH are actually in the normal range but the protein does not function properly.

And type three is very rare in it's incidence. But all 3 types have similar symptoms.

In terms of mechanisms of three types of HAE, the first two types, one and two, have genetic mutations in a gene called the SERPING1 gene. The SERPING1 gene controls the body's production of C1-Esterase Inhibitor protein, which is a protein that helps the body to control inflammation and also has activity in the blood

clotting process or cascade. Without adequate levels of functioning C1-Esterase, a protein fragment called a peptide, called bradykinin is generated. This bradykinin promotes swelling edema by increasing the leakage of fluid from blood vessels into the body tissues. And mutations in the F12 gene are one cause of type three HAE.

For management of HAE, the most urgent aspect is if the patient has a laryngeal attack, an attack involving the larynx, the voice box, and this, as I mentioned, can cause asphyxiation, suffocation, so that's the most urgent aspects of the disease management, but the management of pain and swelling and other attack locations is also very important.

Medical management of HAE can be divided into really three categories, I've listed two: the first is medications to prevent or lower the frequency of acute attacks. We call routine prophylaxis. Medications to treat acute attacks, and the third category would be medication for symptomatic relief of attacks, such as pain

relievers and medicines to combat nausea and vomiting.

Seven medications are currently FDA approved for either the treatment or the prevention of acute HAE attacks. These include, first of all, medicines for routine prophylaxis, can lower the frequency of attacks. An older medicine called DANAZOL, which is a type of anabolic steroid, an oral androgen taken by mouth. All of the other treatments are given by injection either intravenously or under the skin, sub q. CINRYZE is an intravenously, plasma-derived C1-INH. HAEGARDA is a subcutaneously plasma-derived c1-INH so that's given by injection under the skin.

The FDA approved medications for treatment of acute attacks include BERINERT an intravenously plasma-derived c1- Esterase Inhibitor. So like CINRYZE, this derived from human blood plasma. KALBITOR, whose generic name is Ecallantide, a subcutaneously administered plasma kallikrein inhibitor. FIRAZYR, Icatibant,

which is a subcutaneously administered bradykinin-receptor antagonist.

In terms of the beneficial effects of some of these therapies, the FDA approved treatments for routine prophylaxis of acute HAE attacks are effective in reducing the number and frequency of attacks but not necessarily eliminating attacks completely. The FDA approved medications for the treatment for acute HAE attacks have been shown to be effective in reducing the time to the start of symptoms improvement but complete resolution of attacks still takes time. Current medications for treatment of acute attacks have to be given under the skin or by vein, as I mentioned.

Just some of the possible side effects that can be seen with all HAE treatments are listed here in terms of the following three: injections sight reactions, redness, swelling or pain, headache, nausea, fever, and severe allergic reactions can also occur.

But certain HAE treatments have rather specific side effects that are unique to that

particular product. So the plasma or recombinant C1- Estrase Inhibitor products, there is understood to be a risk of blood clots occurring either in the arteries or veins. These can be serious. Liver problems can be seen with DANIZOL. DANIZOL being an anabolic steroid is associated with many of the side effects that are seen with the class of anabolic steroid products including: fluid retention, excess hair growth -- more of a problem for women perhaps, decrease good cholesterol levels, headaches due to increased pressure in the head, abnormalities in the female fetus if taken during pregnancy - that has a box warning and is very important consideration when prescribing the medication to women of childbearing potential.

So in summary, HAE is a serious disease with recurrent bouts of swelling, affecting the gastrointestinal tract, face, mouth, tongue, throat, larynx, windpipe, extremities, and or genitourinary system.

The swelling of the larynx can be

potentially life threatening. And the typical HAE patient may have one episode of that in their lifetime, maybe none if they're lucky; some less fortunate have recurrent attacks of laryngeal edema.

The oral medication DANIZOL and intravenous and subcutaneous plasma-derived C1-INH are approved for routine prophylaxis to reduce the frequency of HAE attacks, but attacks may not be completely prevented by these medications. Intravenously administered plasma-derived recombinant C1-INH Ecallantide and Icatibant are all approved for the treatment of acute HAE attacks but it depends on the particular product as to whether they're approved for prevention or treatment.

Onset of relief is typically rapid, however complete resolution of systems can take hours -- to potentially -- even days, despite therapy.

So what are still the gaps in our knowledge and opportunities for further research?

We have to admit we still have limited data on the long-term effects of these medications especially related to the formation of antibodies as one example, limited data on how best to determine the optimal dose for an individual patient in practice, limited information on effects of quality of life, on how currently available treatments influence hospitalization frequencies or mortality, limited data on how we should or should not combine different treatments together to achieve a better results with patients, limited data on the use of medications in younger children, some of the products are approved in adolescents and above but the data in younger children are very limited, limited understanding of that aspects that are most important to patients in the current treatment landscape.

So how can you help today? We're seeking your input from patients and caregivers to better understand the impacts of the symptoms, how they manifest with you and the challenges that having this condition has, and the impact of the current

medications on your condition. We want to know from you, your perspective on how you would participate or be hesitant, in a clinical trial depending on their design and other considerations. And we like patient and caregiver input at today's meeting to help guide the design of future clinical trials in HAE.

Here's my contact information and the CBER website, the Center for Biologics Evaluation and Research, of which several of us are apart. The Consumers Affairs branch and Manufacturers Assistant contacts are there as well. Thank you. And I'll give it back to Donna.

MS. LIPSCOMB: Okay, so I want to talk a little bit more about the discussion format for us today. These are our discussion topics; I know we've repeated it. We're going to be keeping questions and topics up during the time we have people speaking so it will always, kind of, remind of us of what we were talking about at any time.

Topic one, are the effects of HAE on you that matter most to you, your perspective on

treatments and your perspective on participating in clinical trials. So topic two and three will this be afternoon.

Topic one is this morning. First we're going to hear from a panel of patients or caregivers and the purpose is to set a good foundation for us so we really have a background on what everyone is up against, and the panelists reflect of range of experiences.

Then we're going to broaden the dialogue to include patients and patient representatives in the audience and that's when I'll be walking around with a microphone and giving you a chance to speak. Because time is limited though, sometimes I'm going to have to cut your comments short. Just want to be aware that we're trying to make sure everyone has an opportunity to speak. If you feel like your time has been cut short and there was more you wanted to say, you are always welcome to send in comments to the docket. I promise you we read those comments and look at them while we're making decisions.

When we ask questions and we come to you we're going to ask that you state your name, but I do want to say that this gentleman with the headphones on is not listening to Hamilton, he is actually transcribing the meeting and it's going to be on our web. So I would remind you to give only the information you're comfortable having on the web. So you're first name, you don't have to give your last name, but again it will be public record so I do want to make sure you know that. When we come back after lunch, I'll remind you of that.

Again, we'll talk a little bit more about those polling questions. Their purpose is to aid in our discussions so I'll ask the questions, you'll have time to vote, we'll see the responses. People on the web, we're going to give you an opportunity to answer as well, but unfortunately our technology does not allow those two to combine, so we'll kind of comment in the room and then we'll ask our medical officers that are manning the web to let us know.

Web participants you can also ask questions in the comment box. There are people that are there to answer your questions or to state your comments to the rest of us. So we are asking that patients and patient representatives mainly are the ones to give us comments. And although not every comment that's on the web will be read out loud it will be incorporated into our main record. Once again you can send your comments to the public docket, it's going to be open until November 20th and you can either share your experience or expand upon something discussed today, your comments are going to be incorporated in our summary report. Any one is welcome to comment and the docket number is FDA-2017-N-3068 and there are a couple of links.

These slides will be on our website so later if you want to go and see it and have the live link, you're welcome to do that. Okay?

MS. VASS: Donna?

MS. LIPSCOMB: So I -

MS. VASS: Donna?

MS. LIPSCOMB: Yes?

MS. VASS: Can we just check and make sure that there aren't any more patients or caregivers that are in the back rows that I haven't been able to movie up to the tables?

MS. LIPSCOMB: Absolutely. Come down. Thank you. I would also say that I mentioned that you could go out to kiosk at our first break but someone who looks closely at our agenda sees that we don't have a break so I would suggest in between, once our panelist have spoken, if you have not had an opportunity to order your lunch you can kind of quietly go out and get it before there's a big rush for that. Okay?

At this time I'd also like to mention we're going to start the polling questions and people on the web I think I mentioned this you're going to see two screens, it'll be very clear when we ask demographics first. And for the patient panelists, what's going to happen is I'm going to ask the questions then I'm going to invite our panel one to come up and sit and then after you

have your chance of telling your experiences, during the rest of the facilitated discussion you may either stay up here you may go back to your seats, that's totally up to you. Okay?

The medical officers on our polling questions are Dr. Ross Pierce and Dr. Stacy Chinn in the back. So they're going to be summarizing what's on the web and reporting on it for us. Okay?

So in the discussion ground rules we want to encourage everyone here to contribute to the dialogue. FDA is here to listen so we we're actually not going to say a whole lot towards the end of every topic discussion. We're going to give the panel an opportunity to ask specific questions based on maybe something that they've heard you say but mostly I don't want you to say, hey they just sat up there and didn't say a thing, this is our chance to hear from you. We've got out listening ears on.

Your views today are your personal opinions and you are entitled to them and we want

to hear them and mostly, and so far, what I've gathered here, respect is paramount and we know that that's what we'll get from everybody.

So our first question, if you get your clickers out, where do you live? A city, town, suburban area, rural location?

My little cheat is that I can see the polling questions numbered so I feel like 14 responses is probably not a good number, going to give a little more time. This is the time, people on the web, you're now seeing both this question and your polling question open. Okay, I'm going to give everybody one more minute. And when I say minute I meant second.

Okay. Well, 51% are from town or suburban areas so with a mix of the city and rural.

Our next question, have you or a loved on been diagnosed? Yes or no? This is the wonder Bluetooth notice, so takes a little bit of time from you voting and it coming up here. Okay. Seem to be done at 47. Well who couldn't have seen that

coming at a public meeting specifically for this?

DR. PIERCE: So I'll just mention the web participants had three quarters of them answer no.

Ms. LIPSCOMB: Ah, that's interesting.

DR. PIERCE: And on the last question about 57% were in towns or suburban areas.

MS. LIPSCOMB: Thanks, Ross. I was originally going to come at the very end and summarize it so I don't want you to think I'm forgetting about the people on the web. I should have said that ahead of time. I apologize.

This is a tough one. Female or male? Some of the questions are much more complicated, some are like, yay I can answer it. And all words I can say. Okay, it's 77% female, 23% male.

Our next question, what is your age in years? So, 20 or younger, 21 to 40, 41 to 60, 61 or greater? And no one's going to see this so it's not like you're telling your age. If I was taking this, I'd be in B of course.

Okay. As you can see, 50% are in our 41

to 60, but we do have 9% that are 20 or younger and 24% in our 21 to 40.

And how many years have elapsed between the time you were experiencing symptoms and when you were first diagnosed? Less than 1 year, 1 year or more but less than 3, 3 or more but less than 5, 5 or more but less than 10, or more than 10 years? And that's from symptoms to diagnosis.

All right. Let's see what we have. Ah, 54% more than years. That's incredible. You must have really felt like

you were losing your mind or people - one of the things I read when I was looking online was that people were told that they were crazy or it was in their mind, that must have been horrible for you. I'm so sorry.

So for in the room, we have 51% in towns, 98% were diagnosed, majority of you are female, 58% are 41 to 60 -- my favorite age category, just saying -- almost in the next one.

And the symptoms, more than 10 years was 54%. For the web, what do we have there? Is it

similar or

what's the real change?

DR. PIERCE: Basically similar. The male to female ratio was exactly 50/50 among our web participants who answered the question. We are still having just small percentage of all the registered web participants who are voting on the questions though, so I do encourage the web participants to vote on the questions for the next session.

We have about 40% and change between the ages of 21 and 40, around 50% between 41 and 60, and about 7% who were 61 or greater years of age.

We only had responses in two of the categories for the time elapsed since first symptoms until they were diagnosed, about 60% had the delay in diagnosis between 1 and 5

years, about 40% had symptoms for more than 10 years before they were diagnosed with Hereditary Angioedema, a fairly horrendous statistic in there.

MS. LIPSCOMB: Yes. Well, with those

demographics under our belt, what we're going to do now is invite our panelist of topic one to the podium. It's Kelsie, Shari, Michael, John, and Doug.

We ask people who were interested in speaking to speak specifically on these four specific questions: of all of the symptoms you've experienced because of your condition which have the most impact; are there specific activities that are important to you, that you would like to do but you can't; how have you and your condition and symptoms changed overtime; and what worries you most about your condition?

So what we're going to ask our speakers -- they're going to talk about this, I'm going to leave the discussion questions up for you and we'll just go down the line to speak. So I'll let you go first. And you just press the button.

MR. ARDITO: Good afternoon. My name is Michael Ardito and I am the older brother of a kind, adorable, smart, tenacious 7-year-old girl. My sister Katie was diagnosed Hereditary

Angioedema the day before her third birthday.

Knowing first hand the devastating effects that this disease has after watching my stepfather suffer the symptoms of HAE, I was heartbroken. On that day 4 years ago, I became an HAE patient advocate and caregiver.

As an advocate and caregiver for my little sister. I find that the impact of HAE, what matters most to her, is drastically different than what matters most to me. From the outside looking in the symptoms she experiences from a stomach attack seems to have the biggest impact on her life.

When she suffers a stomach attack, she screams and cries for hours, while vomiting because the pain is so unbearable. Watching her experience this pain and feeling helpless is something I don't even have words to describe.

However, when I ask Katie what symptoms matter most to her she answered without hesitation, when my face swells up because it makes looks like a monster and I'm not pretty. I

was surprised and sad to hear that the emotional effects of HAE are even more impactful to her than the physical toll.

While HAE has taken a physical and emotional toll on Katie, my parents encourage her to participate in everything any other child would participate in. She plays softball, swims, dances, attends school, and plays with her friends. These activities do not make her symptoms worse but she does miss more than healthy kids her age do. She has missed school, sports games, holidays, and play dates because of swelling.

She has been hospitalized for facial and throat swelling, but has also suffered from swelling in her hands and leg.

One of the toughest things about HAE is the unknown. Katie can swell without warning and for what seems to be no reason at all. The unpredictable nature of this disease makes it difficult for Katie and for our family to live without fear and without worry.

Katie has only has symptoms for 3 years

but I'm aware that HAE tends to get significantly worse especially for females during puberty. It is my hope that she will have access to less invasive prophylactics and life-saving treatments by then.

HAE patients in general need more treatment options and easier access to medications. Just days ago, due to a stop in production, we found out that my stepfather has no access to the medication he has been relying on.

In many ways I feel like I am in a race against time. I so desperately want my sister to live a normal life and to be able to do the things I did when growing up.

In conclusion, let's talk about the elephant in the room. My biggest fear is that HAE could take my sisters life. My stepfather was previously intubated after suffering a throat attack and the thought of that happening to my little sister is agonizing.

I also worry that HAE could hold her back from the things she wants to do with her life. And finally after speaking to her about the

symptoms she feels are impactful I worry that she will never be able to see herself as beautiful and that she will always see herself as a monster. Thank you.

MS. STARR: Hi, my name is Shari Starr. I hope I can read my own writing actually. Is this on? Okay, bring it closer, okay. My printer had issues and it's like a font of 5 so if I squint that's why.

I just wanted to thank the FDA for allowing us to come and share our stories. It means a lot to us to be heard. You know, pain is not something anybody chooses and it's definitely not something you want to be apart of your life, but I became familiar with pain from a very young age.

At 11 my HAE started. Living with pain has been unbearable at times and my swelling happens throughout my body. I've been swollen in my face, my hands, feet, legs, my throat, my stomach, intestines; pretty much anywhere that you can swell I've been swollen.

You know, when I have my hands swelling it's very debilitating, it's painful, and it's really uncomfortable, but probably the worst attack and location I can think of is when it's in my stomach. The pain is unbearable and if I had to describe it, it almost feels like someone has just ripped open my insides and is pulling and squeezing my intestines. It lasts for three very, very long days and the only thing that would help is just laying curled up on the bathroom floor and just praying to God that it will end.

It took 10 years to get diagnosed and even after that I didn't have proper treatments, so it was a lot of years of suffering. And, you know, this pain that I'm talking about? I am actually familiar with what it feels like for the general population to know what pain is. You know, I've birthed two babies without epidurals and I've actually even had a kidney stone and that's no joke. So, I do have a high tolerance for pain and this pain is not something that - it's above a 10 on the pain scale.

So during these attacks, you know, like I said, I'm just curled up in the fetal position and I can't eat, I can't drink, you basically vomit every little bit that's in you. You're just in agony and eventually these attacks will end in about 3 days, but then you think okay this one is done, when is the next one going to happen?

And so you live with this constant fear of it looming over you. Can I plan vacation, can I go to my daughters recital, when is the next attack going to happen? And so to live life, to dream, to make plans, to have a future, it's hard.

So planning things it was like a 50/50 chance of okay, I won't get sick, I can go, I can do this, but that does impact your life, it impacts your relationships. It harmed friendships that I had, you know, people were wondering why I always canceled out on them. It impacted me being a good wife and a mom because I spent half of my time in bed.

Probably the biggest impact was just how it stopped me from living. I couldn't go to

college, I couldn't play sports when I was young, I couldn't even hold down a job. It had control of every part of me.

So you say, okay these attacks, the pain lasts three attacks, that's great it's done with, but like I said, I would get these over and over again and if I count, you know, I would have about 3 to 5 attacks, sometimes more, a month. So if you add those days up, that's 9 to 15 days out of the month that I'm sick and that I'm in pain and I can't take care of my family and I can't work. That's practically half of my life that's been affected by HAE. And this is no way to live.

I've missed out on a lot and my family has missed out on a lot because of me. But thankfully, I have been on a new treatment and it's greatly affected my life. And just to compare the difference, it's like now I can live life without worry of an HAE attack, and I can go to college which I'm in nursing school, and I'm living and working and being a good mom and a wife that I never thought was possible.

So I am so appreciative for these approved therapies. And having my mom and my daughter also having this condition has made me really passionate about advocating for this community and I just want to keep striving for better treatments for everybody and more research to be done.

So I just want to thank you again for having us and letting me share my story.

MR. SELSOR: Hi, my name's Doug Selsor. I've suffered from symptoms of HAE most of my life. I recall it started out at the age of 3 or 4 with, you know, the occasional bouts of abdominal stress; they would last a couple days and maybe happen once or twice a year.

Those continued all through childhood and my teenage years and into college. And those were the primary symptoms I had, just the abdominal ones. Occasionally they would -- when I was in college, I ran track and cross country, and sometimes hard workouts or races would trigger the abdominal events and they'd last a couple days.

But, you know, I just thought it was just my physiology or something.

They started to get worse in my early 20's. They would get worse, they would last longer, they would happen more often. As I started working after college I would have -- it would probably happen once a month -- the abdominal attacks, and last again between 2 and 4 days. And I would tend to work through them.

About that time I would start to have, you know, these mysterious bouts of extremity swelling like a hand or a foot. Obviously they didn't -- you know a hand or a foot swelling doesn't seem to have anything to do with a stomach ache so I didn't really tie them together.

Then at the age of 29 I ended up in the hospital for the first time with an airway event. We thought it was -- my throat was swelling shut due to some sort of allergic reaction. So that was the first time I actually ended up in the emergency room.

At the time I was referred to a local

immunologist in Des Moines and along with testing me for various allergens, he also tested for Hereditary Angioedema, so fortunately the first time I actually saw treatment for my problem, I was diagnosed.

But the only treatments available were androgens at the time. So I went on -- during the time that I was able -- I was diagnosed and the time that the treatments were available, I went on to have a number of different hospitalizations primarily for airway events and during that time I was intubated 6 times.

Those are the attacks I fear the most because those are actually life threatening but the ones that impacted me the most was the abdominal episodes. Those were happening more often, I would have at least 1 a month, you know, probably between -- depending on the time -- 3 to 10 days of debilitating stomach pain a month and it affected me, most I think at that time in my work life.

They would happen at inconvenient time.

You would feel that your colleagues couldn't depend on you. They understood the disorder, they understood my disease, they understood the symptoms but in the back of my mind, you know, when I had to cancel out at the last minute for something or I was not able to show up for work, you know, it effected me because I was imagining that they couldn't depend on me.

I also worked for a small business at the time, and it was almost -- because of my constant trip to the emergency room, it was almost a yearly event that we had to switch insurance companies because our rates would always go up so much.

Also, there were times when I couldn't travel or couldn't travel at the last moment. And on several occasions we lost, you know, a bit of business because I was unable to travel

-- not being able to take part in all the events that -- all the activities that kids like to take part in, because, again, something would come up for the weekend and I'd be in bed

with an abdominal attack.

So overall, I'm glad we have treatments now and they're getting better, but as far as my experience with Hereditary Angioedema, those are the symptoms, the abdominal ones, even though laryngeal ones are life threatening, the abdominal ones are the ones that I think have really impacted my life the most.

MS. NEAHRING: Hi, everyone. My name is Kelsie Neahring. I'm 20 years old. I was diagnosed with Hereditary Angioedema when I was 14 years old.

My first memorable attack was when I was ten years old. I was in the dance studio practicing a routine and I stopped breathing. From there, I was taken out of the studio and sent to the hospital with my mom and diagnosed with asthma and an allergy to Ibuprofen.

Then I had continued swelling for about four to five years that was diagnosed improperly in my freshman year of high school after I had my tonsils removed for constant strep throat. It was

actually just swelling. I began to swell every day. I was unable to attend school. I was unable to partake in after-school activities and dance.

So for me unfortunately diagnosis with Hereditary Angioedema didn't bring me relief, because I was a child.

I have the normal C1 inhibitor, so being young and having that rare form of Hereditary Angioedema brings additional challenges when attempting to seek out treatments.

My worst attack was -- my sophomore year of high school I was hospitalized for almost two weeks. I had a 19-day attack with no relief, no pain medication. I was just laying in bed in pain for almost a month.

Then also I think it's important for everyone to remember that the symptoms of HAE aren't only physical. I suffered socially and emotionally.

It's so hard to live as a kid with this disease. I never thought that I would graduate high school or move on to college, but fortunately

I was able to get on a treatment plan before I left for school and it seemed to keep me pretty well controlled.

I just want to say that I'm here on behalf of the young kids that can't be here. I had the opportunity last weekend to meet with so many young people at the summit that are affected by HAE. So many of them are ready to give up. It's not okay.

So I just ask everyone in this room that we push for treatment for kids and research for kids, because I don't want them to live in the childhood that I did. It's not fair. Thank you.

MR. WILLIAMSON: Hello. My name is John Williamson. I have suffered with HAE most of my life. I was diagnosed as an infant by the Navy when my mother received her medical discharge due to HAE swelling.

Well, all types of HAE swelling can be uniquely disabling. Laryngeal swelling has always been my and every HAE patient's worst fear.

After watching my mother's throat close

to the point where she needed to have an emergency tracheotomy in our living room when I was seven years old, I became very aware of the power that HAE has. I have witnessed most of my family members at one point hooked up to ventilation, ventilation tubes and tracheotomy tubes. I experienced my first laryngeal swelling and was hospitalized at 16.

This fear is something that we think about every day and often the last thing that we think about at night. So it definitely comes with its emotional and psychological toll as well.

Before having access to treatment, there was a lot of physical activities that seemed impossible. I always loved playing sports, but being hit with a baseball can lead you to an ICU visit with facial and throat swelling. Attending school was always hard, not only due to the absences of being sick, the embarrassment of going to school disfigured and swollen, but also the distraction of not being able to focus on your work when you're in so much pain.

Missing work has always been an issue. Most employers are not very empathetic to the fact that you're sick and they don't really understand the severity of HAE swelling.

Luckily my family has always understood when we miss family events due to HAE swelling. Like I said, most of the members of my family do have HAE and it's just something we all share.

Having access to treatment has completely changed my life. I'm now able to control my HAE for the most part. I'm able to work. I'm able to live somewhat of a normal life. I'm not forced to live on disability programs. I am able to continue to contribute. So life for me is slowly getting better with HAE.

I do still worry, because I do still have breakthrough attacks. Even with access to prophylactic treatment and acute treatment, I still had a breakthrough laryngeal swelling in January. I do worry that I will have a laryngeal swelling in my sleep and won't wake up. Or if I do wake up, it will be too late to be able to

treat.

I worry about the fast moving abdominal attacks that disable me and keep me from being able to work, keep me from being able to contribute to my family. Most of all, I really worry about becoming stagnant in my treatment. We need to continue to move forward and progress and continue to strive for better treatments and a better life with HAE.

MS. LIPSCOMB: Thank you, guys, for your experiences.

How many of you in the room heard your experience in something someone said? Wow. We're going to talk -- have an opportunity to talk a little bit more about that.

Does anyone want to give a little -- say your first name again.

MS. RAMSEY: Hi, everyone. My name is Adina. I am an HAE patient and today is the eight-year anniversary of me being intubated with a laryngeal episode. So at this time eight years ago, I was in a medically induced coma and I

legitimately thought I was going to die in front of my mother.

I think that kind of resonates with me with that experience as how easy it is to be written off by doctors and emergency rooms and in urgent settings.

When I had that episode, I went to the ER of my local college. It was a middle-of-nowhere town in Kentucky, and the doctor tried to treat me with Benadryl and told me to wait. Everybody has a story of a doctor telling them to take Benadryl and wait. I said that wasn't good enough, and I was sent to a different hospital.

So something along with trying to find research for kids and trying to develop effective treatment for kids is also trying to raise awareness with the physicians that we encounter on a (inaudible) basis, so that's kind of my contribution.

MS. LIPSCOMB: Thank you. Well, I think we have a great basis to begin our facilitation.

Chris, could you hit the next --

So the next question I'm asking everyone to kind of talk about so we can hear more is: Of all the symptoms that you've experienced, which are the ones that have had the most significant impact on your life? You can choose up to three.

This is that great time where I told you you have to look at the number, watch it disappear, and then pick another one. So it's the watching it disappear is the important part.

I want to remind people on the web to respond as well. Slowing down, we're going to give everybody another five seconds. Chris, can you show us the results?

So hoarseness and abdominal pain, and this set is the most prevalent followed by vomiting. I think that's what it says. How does the web look? Is it similar?

DR. PIERCE: It's pretty much an equal split between hoarseness, throat swelling, or difficulty breathing, swelling of the face, and swelling of the tongue with just one other.

MS. LIPSCOMB: Thank you. So does anyone have an experience with swelling in one of these places that you'd like to tell us about?

MS. KLINGER: Hi, my name is Lydia. I have a story that I know some others share. I had my first severe abdominal swell as a grown person who actually knew what was going on when I was 18 in college. I had started taking birth control pills like many young girls do not knowing that that was going to be a trigger for an abdominal swell.

So I went to the emergency room in my college town, an hour and a half from home, and was given an emergency appendectomy, because no one knew that I had HAE and that was the best thing they could figure out what was wrong with me.

So what they ended up finding was two liters of fluid just sort of hanging out in my abdominal cavity, and then my mom showed up and said, oh, yeah, you were diagnosed with that when you were eight years old. I was like maybe you

should have told me that.

But that is something that I think we all share, and kind of going back to what Adina said, is going to the hospital, especially when it's new and you don't know what it is, and being completely misdiagnosed.

MS. LIPSCOMB: Thank you. Does anyone else want to speak? Thanks.

MS. BRAHEN: My name is Peggy. For the most part, it's just hands -- it started with hands and feet with me. You think, well, hands and feet are nothing, but if the bottoms of your feet are swollen, you can't walk anywhere. And if your hands swell up like a balloon, it's like -- man has opposable fingers and you can't pick stuff up, you can't like pull up your pants. You can't do anything, dress yourself, feed yourself when your hands are swollen up. When your hands and feet are both swollen, you basically can't do anything except just sit there.

So you might think -- I've also had internal too, but hands and feet more, but they

make your life miserable just as well.

MS. LIPSCOMB: Donna.

MR. CASTALDO: Thank you. My name is Anthony Castaldo. Picking up on some of the themes of our panel here, I think many of us will identify with the fact that upon arriving at the emergency room and people not knowing what's going on, we're often labeled as drug seekers.

I have one -- the HAE group had a patient summit meeting a week ago, 800 of our best friends were there. It's amazing to see this wonderful attendance here, given the fact that everybody was out in Minnesota just a short week ago.

But at the summit, just to leverage off and further discuss some of the things spoken about here, not only did we hear a tragic laryngeal attack story that just happened not too long ago, but it's really interesting in this ramification, because this patient actually knew he was having laryngeal attack, didn't have access to therapy at that moment for a variety of

different reasons, and crudely tried to fashion his own tracheotomy.

Luckily the paramedics got there in time and they were able to save his life, but he actually was -- he was actually arrested by the police and put in for a psych consultation.

So these kinds of things do happen and this really does show the severity of this disease and how it's still at this juncture very much misunderstood out there in the medical community.

MS. LIPSCOMB: Lonnie, do you have someone?

MS. BARNES: I'm Jenny Barnes from North Carolina, you'll probably figure that out if I talk long enough, but I want to give you perspective from a caregiver side.

My son was diagnosed at the age of five at Duke with HAE Type I. He passed away in June 2008 from a laryngeal swell while he was at the emergency room waiting for treatment.

I'm looking at your list there and we're supposed to kind of prioritize, and I know it kind

of gives you a gauge of where you -- but as a mom, any one of those things caused him a disruption in his life. He couldn't put his shoe on. The little fellow at five years old, I would have to put him in sweat pants because he couldn't get his little pants buttoned.

He would, to your point, Mike, walk around. And his face would be just swollen enough on one side to make him look disfigured. He'd look at me and say I can't go to school. I look like a monster, and he was in kindergarten.

So these are the heart breaking realities. I am the reality of having been trying to be on top of conferences and doctors and all this. I was involved in everything and he still died, so that's the reality.

Anything on this list is a disruption in your day, even if they just say other symptoms or seven percent of going to the bathroom. Everybody knows how profound that is when seven percent you can't go to the bathroom, in that moment that's a hundred percent. So that was the point I wanted

to bring up. Thank you.

MS. LIPSCOMB: I appreciate that. We have another person.

MS. EDWARDS: I got the nerve to stand up and talk. My name is Carol Edwards. We talk about abdominal pain, well, when I was pregnant they said how bad child birth was going to be, it was nothing compared to an abdominal swell, which I -- it took me

years to get diagnosed, so I had no clue what it was.

So I'm really realizing today what that pain really has been like. I never realized it, because I was young enough back then to be able to get through it. I'm older now, I can't get through it anymore. I've got to have help each time.

The other thing I want to add is that you've got on F nausea and vomiting, you don't have diarrhea. Because let me tell you if it's coming up one end, it's coming out the other and it's bad. You can't control it. It's just there,

and that's bad.

Because in my luggage, I pack lots of underwear and it's really not funny, because you never know when that's going to hit. You can't make it through it, so I think that's important to have on the list of symptoms also.

MS. LIPSCOMB: Well, thank you. That actually touches on a point, are there symptoms when we have kind of other symptoms not listed that you'd like to mention. Before I get to you, I promised you.

MS. HARVEY: Good morning. My name is Tiffany Harvey. I've been intubated three times. The first time I swell, I was 18 months -- I'm sorry to get emotional, because it's really stressful.

In 2016 when I was pregnant with my daughter, it was a very difficult pregnancy. I stayed sick the whole time. She was three pounds, but I was able to carry her full term.

Because of the Angioedema, it took a lot out of me. Just recently, just a year ago, I've

been on a new medication and it has improved my life tremendously. Just dealing with Hereditary Angioedema since 18 months, it's really been hell, so I've been through it all. I think it's very vital that we continue to do the research, because it's needed. Thank you.

MS. FRENCH: Hello. I'm Cheryl. I am a Hereditary Angioedema patient as well as a caregiver, because both of my daughters have Angioedema as well.

The FDA is a data driven bank of information. I would like to share with you some of my data. I was

when I started swelling. I waited 16 years for a diagnosis. I'm celebrating my 20th anniversary of having a diagnosis, but I've only had five years where I had treatment where I could continue a normal life, if "normal" is a word that we can even use in this family.

In one year I was admitted in the hospital 184 days. A school year -- I'm a teacher. A school year is only 180 days long, so

184 days admitted in the hospital. That's not including clinic days, going back and having test results, CT scans, abdominal sonograms, biopsies, the report after they did my surgery and took my appendix out, because I was diagnosed with appendicitis.

I've lost one child due to abdominal swelling so severely throughout the pregnancy. I have lost 14 jobs because of this disease. I have had three deaths in my extended family because of laryngeal attacks. In one month, I incurred $384,000 of medical debt. This has affected my entire life and this is a disease that I carry physically in my body, but I physically also carry emotional. It's like I've been diseased emotionally as well, because of all the things that this has impacted in my life. Another thing I carry as a parent is guilt, because now it's my babies.

I'm here today for two, that's my big number today is two. Because of my two daughters, I need more. I'm begging you to go with those to

continue this fight, because I've truly only lived ten percent of my life. Only 10 percent of my life has been somewhat normal.

MS. LIPSCOMB: Thank you. I'm going to jump in here and I'm going to sound -- we have a lot to ask, so we're going to try to keep the discussion points on what the questions are. I think there will be times to hear all of your experiences, so please don't feel like I'm cutting you. We're going to hear one more person and then we're going to go to our next discussion question. I'm sure there will be a time for you to be able to do that.

MR. EDWARDS: Thank you. My name is Miles. My wife has HAE. As a teacher, I have discovered a couple of students with it. One case in particular I know absolutely it was HAE. Trying to get assistance for that family, trying to get the family to understand what's going on was next to impossible. Educating the school nurse was next to impossible. When she did figure it out, did the research she was like, there are

more kids out there that we need to discover and we need to discover the kids in the school system, because the monster effect that was pointed out is crippling so many kids, because they swell up, they feel like they're monsters, and they don't need that. So please help us find and discover these kids, because there's a lot more out there than what we have numbers on right now.

MS. LIPSCOMB: Thank you. I don't even know what to say. Your stories and experiences are so moving. Let's get some more questions, facilitated questions, and we can get some more information from you.

So have you experienced one or more vomit attacks involving your throat, yes or no?

Chris, can you -- wow, 89 percent. What is the web numbers?

DR. PIERCE: We have just four responders, three said yes, one said no.

MS. LIPSCOMB: Thank you. Let's go to the next question, because I think it leads into this. If you answered yes to the previous

question, was a breathing tube inserted into your windpipe.

So 29 percent did, 71 percent of you did not need -- does someone want to talk more -- who would like to share their experience with --

MS. LONG: Hi, I'm Janet Long. I just want to point out that the question we have to also understand does not cover folks who experienced a tracheostomy instead of a breathing tube or intubation.

It also does not cover those who may have been undiagnosed and did not even know that they had the option of going and having that take place and were fortunate to actually not have their throat close all the way. So it is good information, but you also need to know there are other factors.

MS. LIPSCOMB: We'll add that to our conversation as well.

MS. PEREZ: Hi, my name is Brittany Perez. I have HAE. I'm a patient. I had my first swell when I was seven. My main issue is --

I have issues with urination, because the swelling and doctors don't seem to understand that.

So when you go to the hospital and you try to explain that to a doctor, they don't -- because of issues, you start to throw up and your stomach starts swelling and it causes other issues with your HAE.

So they stick a catheter in you. A catheter, they tell you to relax. They tell you, well, you're worrying, relax, you're making it difficult. You're tensing up, and and it really hurts.

When you try to tell them it's not that, they tell you you're lying, it's not HAE, it's something else. My one experience, the nurse just shoved it in and it -- he's like, well, I can't get it in. He's like, you're making it really difficult. So you got someone else and it took them three attempts. By the third attempt, it just felt like a hot dagger just going in.

When they did get in they didn't get it in correctly, so they had to keep playing with it

just to get the urine out and then they said, well -- they kept asking me what HAE is. I explained it to them. They wouldn't give me my medicine, which they had on hand at the hospital. Instead they did sonograms and they found out there was all this urine retention. They said, well, I'm just holding it and --

MS. LIPSCOMB: I'm sorry.

MS. PEREZ: -- it was such an argument. By the time they got the urine out, they sent me up to Albany thinking it was because of my back. Albany told me, well, that I came up for no reason, I wasted their time. Because there was no urine, (inaudible) sent me.

When they took the catheter out, I was bleeding. I was just so bad. I had -- quite often, I swell from the HAE and this one gets so bad I can't pee for days at a time sometimes, even with medicine.

MS. LIPSCOMB: Thank you for sharing that experience. Thank you very much.

You had your hand up.

MS. BRAHEN: Yes. This is for the swelling in the throat. I never had had it before, and so I didn't know what it was. I'm lucky that I did have Firazyr on hand. I thought my throat was sore. Usually -- I'm lucky, because so far my attacks have started slow and gone slow. I thought maybe I was getting a sore throat and usually the sore throat turns into a cold.

After about half a day, it didn't turn into a cold. I said, well, I'm always -- let me just try Firazyr and see what happens. I'll be darned, within -- Firazyr works for me within five to 15 minutes. Within 15 minutes, it's like I found out it wasn't a sore throat. My throat was starting to swell, so that really opened my eyes.

If I hadn't have had the Firazyr or the options available, then it would have continued up and slowly would have closed off. I knew I had HAE, but again the problem is convincing these doctors and convincing the hospitals and stuff, because they don't want to hear it.

Anyway, it can be slow, but you can --

at least I can control it with the Firazyr, but you have to recognize what it was. I didn't. I thought it was a sore throat turning into a cold.

MS. LIPSCOMB: Thank you for that. Did you have something you want to share?

MS. SANTEE: Hi, my name is Tina and I have HAE with normal C1 inhibitor. I've been intubated three times. The very first time they actually had to resuscitate me, because they had trouble getting the tube down. I stayed in the medical ICU for three days, and this is pre-diagnosis properly. I've spoken with John's mother and we felt that I had it, but the testing came back negative.

The second time I was intubated, I almost lost my life from a secondary infection of staph pneumonia. This was all before medications came to market.

The very last attack that I had was just three years ago. I did have acute medicine, rescue medicine, available. However, because I just recently had throat surgery and was still

numb, I was a little late in administering the medication.

That's why I'm here today. It is very crucial that the FDA continue to fund our research, because for me and the type that I have, I only can respond to my attacks after the fact.

So I too want to be able to have a little bit more freedom. Since the medicines came to market, I have had a little bit more autonomy, but I do fear that I will have an attack that I won't be able to respond in time for.

The very first one I mentioned, the only way that I'm here today speaking to you is because I had an alarm that woke me up and I had just five minutes to get to the hospital, so thank you.

SPEAKER: Donna, I have someone.

MS. LIPSCOMB: Okay.

MS. WHITAKER: Hi, my name is Diane and I have HAE 1. I began really feeling symptoms when I was in probably fifth and sixth grade. I know in sixth grade I missed 65 or 70 days of school, and it was due stomach pains. They would

be so bad, I would just -- would crunch over.

When it first started, the doctor gave me phenobarbital; then another time, the next year, I was on Librium, next year it was Diazepam, or Valium, and the pain just continued, continued, continued.

I didn't get diagnosed really until I was 40. But when I was 18, I had a hemorrhoidectomy, which is not common for an 18 year old. So about five years ago, I was having problems with my sphincter, and she's talking about genital and I'm talking more rectal.

I have a Medtronic device now in my back. Because of all the swelling in that area with my sphincter, it would go out -- it lost its control and the Medtronic device now does, so I can go to the bathroom as a normal person.

But we need to spend so much more time in trying to find other therapeutic ways to help people, because there is no -- when you're having these stomach attacks and when you -- you almost feel like a guinea pig, because it's -- it seems

like it's always something, always something.

Like this last week, I had an ultrasound of the stomach. They wanted to do a -- I feel like there's knives in me at different times. It happened in the middle of the night. They want to -- the doctors don't understand.

I'm a huge advocate. I'm going around to as many hospitals, colleges, especially anesthesiologists. I had an anesthesiologist once -- I was going in for something minor and the anesthesiologist said, I'm not treating -- I could hear. I'm not treating that HAE patient. Why didn't anybody tell me. And I stayed calm. He came, I'm giving you FFP and steroids. I said, no, you're not, sir. I said the order is for me to have the therapy before surgery. I don't want to. I said, but if you look at the order -- I stay calm. I've learned -- I try to stay as calm as I can. They don't.

Then when he went to infuse me, this is a professional, he goes A is for after death, B is for burial, C is for cremation.

I said, okay, I guess I'll join in. D is for death, E is for eternity, and -- a lot of patients might not take it that way, but I had to in order to keep myself calm. We just need to really be able to reach out and educate as many people in the professional world as possible.

MS. LIPSCOMB: Thank you. I think I saw a hand over here. Go ahead.

MR. WILLIAMSON: I'd just like to add a little bit on the breathing tubes. I spent a majority of my childhood communicating with my mother on a dry erase board, because she was constantly intubated, more intubations than I can count.

I think we all know here that there's something extremely terrifying about having to find that right position that you can hold your head just so that you can get enough air in while you're waiting to get to the emergency room. That's it, thank you.

MS. LIPSCOMB: Thank you.

MR. ARDITO: My first experience with

HAE was when I was seven years old and my stepfather had a throat attack. He was put into a coma for almost two weeks. So I guess as a seven year old, it was terrifying. Because he had been in my life for a couple years now at that point and suddenly he was taken away from me, and I didn't know if he was going to live to see the next day, if I would ever be able to talk with him again. Thank you.

MS. LIPSCOMB: Thank you.

MS. EDWARDS: I'm Carol. About a year after being diagnosed with HAE, I had a crown done at the dentist. After going to the dentist I went to target to buy some wine, because I was going on a cruise. I'm not feeling too good.

I'm going no, no, this can't be a throat attack. I thought I was immune to it, because I only had the abdominal kind. We're not immune to it, so I picked out my wine. I said, well, I'm not going to an ER, they'll never believe me. I went home and that prompted me to be able to go to the doctor and say, maybe I need some meds in case

I have a problem. He said, well, did you go to the ER after you had your throat swell? I said, no, I wasn't going to go. He said, you were really stupid.

So I do admit that I can have laryngeal swells and I'm not immune to it, and that takes a lot for someone like me, so anything can happen with this disease.

MS. LIPSCOMB: Thank you so much. This will be our last one, then we'll move on to our next question.

MR. VENTURELLA: My name is Steve and I am a caregiver, I'm not a patient. Our son -- is not the patient, it's my wife -- is on the Autism spectrum. Every time something like this would happen, and it happened a number of times throughout his childhood, he thought his mom was going to die. So this has always been something that we have been dealing with. Even as an adult, he still struggles with it.

I just want to echo what so many others have said. This opportunity for research through

the FDA, please continue. Please advocate through your local communities and hospitals and physicians. It's really critical. Our son has turned out quite well, but it impacts more than just the patient. It impacts the entire family. I think it's really important that we all are aware of that and that we continue advocacy.

MS. LIPSCOMB: Thank you so much. I want to give people on the web a chance. Are there any comments that were written that you want to --

DR. PIERCE: We're not getting any comments.

MS. LIPSCOMB: Web, what's up? This is me talking to the web, so my back's not to you guys.

If you're on the web and you are having issues, please log out and then log back in and that should help. We do want to hear your comments, if you have any, on the web, so please, please, please go ahead and feel free to write comments.

We're going to go to our next question: Have you ever had an attack that was treated in the hospital?

(Indistinct chatter)

MS. LIPSCOMB: So 95 percent of you have. I'm going to ask the second question, then I'll come to you guys.

The second question is: For those 95 percent of you if you answered yes, how many times over the past year have you been in the hospital, one time, two to five, or more than five times?

(Indistinct chatter)

MS. LIPSCOMB: That was for if you answered yes to the last question.

(Indistinct chatter)

MS. LIPSCOMB: Was it ever -- okay. In my mind, I will do a show of hands for zero, how about that. These slides make so much sense when you are talking about them and not living them, so I apologize for that. Thank you for bringing that up.

We'll give those answering -- well, I

think that tells us the answer there with the 13 people responding.

Chris, can you go ahead. For those of you who were, 38 percent, one time; 38 percent, more than five times. Wow. How does the web -- did we have any responses?

DR. PIERCE: So three out of four for the Question 9 had been treated at some point in the hospital. For the four responders to Question 10, they all had been hospitalized between two and five times in the past one year.

MS. LIPSCOMB: Thank you. I'm presuming, but I don't want to do that, we all know that cute little acronym.

How many of you have not been in the last year but previously, right, okay, thank you.

Well, I want to know if anyone wants to talk about their experience -- well, sometimes I just think it's silly for me to ask the question. I just should say, who wants to put their hand up.

MS. FRENCH: Well, between Question 9 and Question 10 and because of the work that we

have all done together, our lives have improved so much in the last five years, that Question 9 really doesn't apply to my life anymore, and I'm grateful for that.

Because as a patient that was 184 days in the hospital in one year, it has now been five years since I've been admitted to the hospital, and that's because of the new treatments, the new medications, an excellent doctor that works with our family, a diagnosis, and finally getting to live that life. So Question 9 and Question 10 thankfully apply to the old me.

MS. LIPSCOMB: Thank you. I appreciate that. Kind of clarification. That's good for us to know.

MS. URBANIAK: Well, my name is Sally and I was just going to -- kind of to your point, when people ask my how do you live with HAE, it's like it's two different worlds. There's like one before therapy and then one after.

So I would say the same thing. Since therapy, I have not been to an ER or hospital.

Before that, totally different story.

MS. LIPSCOMB: Thank you. Let's go to someone who hasn't spoken. We'll get back to you.

MS. BREADY: Hi, my name is Regina. I have Hereditary Angioedema Type II. I was diagnosed at 35. Nobody in my family has it. I'm the only one.

But I just want to say the impact of research for the way hormones affect our attacks, I am going through menopause right now and I've been going through hot flashes. Since September 2nd, I had ten attacks, three in my throat, three in my face, and other parts of my body.

With the therapies that we have now, we need more therapies. Because when a therapy gets stuck in a place and we can't get another therapy, it's important we have access to things that are going to help us.

I'm on a waiting list right now, so I can't even get preventive medicine right now because of the backup. So it's so important that we keep doing this research and finding out better

ways to help us, especially when we're going through different changes of our life, so thank you so much.

MS. LIPSCOMB: I'm going to jump behind you and I promise you you are next.

MS. YODEN: Yes, my name is Denise and my father had HAE and suffered terribly with it for years. I watched him suffer in bed and agonize so badly that if anybody even sat on the bed, it just -- he was in excruciating pain just from the small movement of somebody else sitting on the bed next to him.

They told him that he it was all in his head. They opened him up, did exploratory surgery, sewed him back up only to have his stitches burst after he swelled, because of the trauma from the surgery.

My sister and I are the only two children my father had and we both have HAE. My oldest daughter, I have three girls, she has it and she has two boys and her youngest son has it.

As a child, I mainly had it on my outer

extremities. If I would go swimming, snorkeling, just going into the lower depths of the pool, the pressure, wearing a snorkel and a mask, the pinching, my lip between the snorkel and the mask would cause my face to swell.

I would mow the grass, my hands would swell, that sort of thing. When I started having my children, I started having attacks in my stomach. Of course you can't take any medication. I couldn't take the Danazol, the Danocrine at the time when I bearing children.

So when I finished nursing my youngest daughter, I got on the Danazine, Danocrine, Danazol, and it changed my life. So I was on it for 32 years, had a wonderful life, could manage, and then here recently I went to the doctor and he said that my cholesterol was a problem, an issue, and that I would have to get on cholesterol meds.

I didn't want to get on cholesterol meds, so I said, can I get on the Berinert, so I got on the Berinert and I've been on it for about three months now. I've given myself the IV and

it's going very successfully.

But when we were at the summit, I heard about the HAEGARDA and I'm real excited about that, because it's subq and I'm just so thankful for all the new options that are out there for us.

I'm so thankful for the opportunity to be here today and to plead our case. I hope that you will listen to us and have sympathy for us and for our needs. I just am so privileged to be here. Thank you.

MS. LIPSCOMB: Don't want to go back on a promise.

MS. EDWARDS: I've never been accused of talking too much, trust me. When I see these two questions, Question 9 and 10, and talking about being treated in the hospital, what kind -- what do we mean by "treated"? Were we treated with the proper medications, with something that's not going to work, and was it in a timely manner, and I think it's no for a lot of us.

So being treated with the proper way really means a lot. I wish on these -- the rescue

meds, or whatever, for HAE that they put in "needs to be administered in a timely manner, otherwise it's really not that effective", because you just can't get that across to the medical professionals. I'm a nurse and you just can't tell them. They don't care.

MS. LIPSCOMB: Thank you. We're going to take one more comment and then we'll go to our next discussion question.

MR. CASTALDO: Thank you. I would dare say, though, from some of the comments we have, but even some of the research that's been done, notwithstanding, we'll get into this I guess when we talk about treatments.

Notwithstanding the availability of current therapies, we still do see a fairly significant burden of illness for the reasons that folks have talked about before.

Non-demand patient still has distress associated with whether or not they're going to have an attack, whether or not they're going to be able to treat it in a timely manner. I thought it

was very articulate some of the folks on the panel talking about if you wake up in the morning, will you wake up, will you have a laryngeal attack.

So I just want to make sure that, yes, we do have therapies and we'll talk about those. Certainly it's changed many of our lives, but there is still a significant burden of illness out there. I don't want that to be eliminated from our discussion.

MS. LIPSCOMB: Absolutely. In fact, we are actually running ahead of time, so it seems to me that some of you would like to talk about either treatment -- I mean, not treatments, because that's this afternoon, treatment's this afternoon, but symptoms that maybe we've not talked about or issues.

I think I've seen your hand. Let me get you, then we'll come over here.

MS. THOMPSON: Hi, my name is Dakota and actually five years ago today I was diagnosed with HAE. It took me about six years to be diagnosed. Through all of this, the other most debilitating

symptom is actually mental health. I suffer with depression, I suffer with anxiety, and it sucks.

It's not a traditional symptom, but we're afraid of when our next attack will be. We're afraid of how we're going to be treated.

I remember before I was diagnosed, I didn't even want to go to the hospital. My pain was ten out of ten. I didn't want to go. They couldn't do anything and they were just going to accuse me of drug seeking. Even now I've been diagnosed for five years and I have a really great doctor, and I still don't want to go to the hospital, because I'm afraid of what they're going to say to me. I'm afraid that they're going to say no and, like so many others, die from a throat swell, because the doctors don't believe what we have.

On a day-to-day basis, I have no social life, because I've lost friends who think that I just want to blow them off. I don't. I want to go out. I'm 25. I want to go to the club. I want to go hang out. I can't, because I'm just

either in an excruciating amount of pain or I have fatigue. Fatigue has followed me everywhere since I was 14, and I don't have the energy to go out even for lunch or Starbucks, so I have no friends.

It took me -- I failed out of college, because I couldn't make it to class. I had to quit my job, because I couldn't hold anything. My hands would swell up too much. And working at a fast food restaurant, you need your hands for every aspect.

It's followed me throughout this whole thing. I'm happy that we have better medications, but now I don't know what I'm going to do with my future, because I'm still so afraid that I'm going to go back to swelling twice a week, every week for two months straight, having to go to the emergency room twice a week every week for two months straight, and it's terrifying.

This is the only other symptom besides the abdominal pain and the nausea that has hit me the hardest. Anxiety and depression are real. The mental health aspect needs to be addressed at

least. Thank you.

MS. LIPSCOMB: Thank you, Dakota. Do we have someone over here? Then we're going to go to the web.

MS. FOX: My name is Debbie. I think one issue that is very common for women is that the disease is often triggered because of hormonal changes. When you are in your teens, you often have your first really bad episodes. For me pregnancy -- I was not diagnosed until I was past all my childbearing years. It was almost 40 years before I had a diagnosis, so I went through four pregnancies extremely sick and all kinds of medications to help with nausea that never worked.

My last pregnancy, my two year old went and lived with my mother for three months because I could not care for her, because I was so sick.

It was that same two year old when she turned 16 and began to have extreme episodes every month that said, momma, I'm not going to live to see what you have lived and thrived (inaudible).

We finally got diagnosis, so I would

like to see a lot more research about -- I guess about the hormonal impacts and how you can adjust medications and things based on where you are in your life hormonally, menopause, all those different aspects of your life as a woman that severely affect the disease.

MS. LIPSCOMB: Thank you. We're going to go to the web and hear some of those comments, please. Stacey.

(Indistinct chatter)

MS. CHINN: So Beth on the web has echoed similar comments that have been presented here in the room, that prior to new medications becoming available, she was in and out of the ER four to seven times a month and this was a big burden on her life.

As well we have a comment from Crystal who has shared a story about being in the ICU for laryngeal swelling. Upon being transferred to the floor, her C1 inhibitor was not continued. After a two-and-a-half hour delay in getting the medication, the nurse ignoring her, she wasn't

able to speak and was worried that she wouldn't live to see her daughter's birthday, which was just ten days away.

So I think has shared similar stories to all of you who have just realized that there is a lack of understanding sometimes in the medical community. It takes too long to get the medication you know you need.

MS. LIPSCOMB: Let me get to you.

MS. RAMSEY: Adina again, sorry for hogging the mike. Something that hasn't been addressed yet is the relevance of using ports or maintaining vein health whenever you're administering medicine. I was very fortunate to have started a prophylactic treatment in 2009 after my laryngeal episode, and I had a portacath implanted.

That port malfunctioned and had to be taken out. I had a PICC line implanted, that PICC line came out. I'm not on my second portacath, and there are other factors to consider when it comes to treating HAE.

One thing that could happen is development of blood clots, and I'm sure all of you are aware, but I think trying to be aware of the method of medication being administered. Obviously subq -- having a pill a day would be fantastic. Subq is a nice compromise and IV is necessary, so I guess trying to aware of other things that go into method of treatment.

MS. LIPSCOMB: Thanks again. We will be talking treatment much more exclusively in the afternoon.

MS. BEITER: Hi, my name is Angelica. I just wanted to sort of go off of what she said too as far as veins and stuff like that.

When I was diagnosed, they wanted to teach my mom how to start an IV on me, and it's a burden on a health care -- for the caregivers and stuff like that. But when a registered nurse can't get an IV in, they're poking you six to seven times for one IV, it's so discouraging to be spending four hours of your every two days to get this IV put in.

I was attending college for a while with IVs in the back of my hand and in my arm, because they were so scared to remove it because they couldn't find another one the next time I needed treatment.

They finally decided to put a PICC line in, but being 19 and not being able to shower normally or swim or play sports or really do anything, lifting, anything like that, because some of us can't tolerate ports and stuff like that. Different doctors think different things don't work.

For everyone to be on the same page would be nice, but it's definitely a burden to be 19 and not able to do things because I can't get my right arm wet. To know that -- like there's no medications coming out that are subq, but some of us aren't approved for it. I know a lot of people too not every medication works for them.

So it's important that we continue to look for different ways to administer the medication as well as being able to still live

life, because at 19 and trying to explain to people I have a tube hanging out of your arm is really sort of an awkward conversation to have, that's for sure.

But it changes everyone's life and everyone has to cope with it differently, because a lot of times doctors won't treat you for other things you have going on because they're scared to interact the medications, because they are not very well known.

So when you go to see a doctor because you think you have rheumatological issues as well, they say, well, we don't really want to kill you, that's really scary.

I think a lot of us in the room can say that maybe HAE isn't our only thing we have going on medically. But to get a diagnosis, a lot of times doctors just stick every symptom under the umbrella of HAE because there is so much lacking as far as knowing what symptoms can stem from HAE.

I know me personally I have so many problems with infections and my white blood cells

don't elevate, but they don't know -- they can't figure out what's wrong. I can't control my body temperature and there's so many things that I've seen -- that I've talked to other patients that we have similar, but it's not considered a symptom because it may not be researched yet, so thank you.

MS. LIPSCOMB: Thank you.

MS. CLASEN-KELLY: Good morning. My name is Liz. I have HAE Type I. I had my first attack when I was nine and I was finally diagnosed at 34 after some unnecessary surgery, many hospitalizations, and much of my life thinking I was crazy. Actually I knew I wasn't crazy, but everybody else thought I was.

So the symptom I want to talk about or the word I want to talk about is "potential". So thank you, FDA, for having this. It's so powerful to get patients in a room. I hope you just get a taste of what an amazing group of patients we are.

So much of the disease for me has been about not being able to live out my potential. So

when I was

-- and I was straight A student. I missed a ton of school. I always made up my stuff. I was -- got accepted into some great colleges. When I was 18, my doctor told me he didn't think I should go to college because I couldn't handle the stress, because my body couldn't handle the stress, which just made me really angry and work all the harder. I proudly have my master's degree from Duke University.

At every kind of stage of better treatment, so once I got my diagnosis, once I got on the modern therapies, now on a drug study, what I've been able to give back to the world at every level is just enhanced. So as I get healthier, there's so much I can give back.

I'm now proudly the executive director of one of the largest emergency shelters in the southeast. We provide emergency shelter and help 350 men every night get out of homelessness. I could never have dreamed of doing this job ten years ago, because now with the modern therapies

and thankfully being able to be on a clinical trial, I can lean into my potential and I don't have to miss those big moments as I did throughout life.

And I -- just get to know the amazing patients in this room and just know the more access we have, the more we're going to give back to this community and to this world, so thank you.

MS. LIPSCOMB: Thank you.

MS. RENDON: My name is Amy. This is my daughter. I'm going to read what I wrote, because I'm not good at holding it together.

With a newborn, they tell you about sudden infant death syndrome. For the first six months of her life, she slept on the couch with my hand on her back, new mom, you know how it is, just to make sure she was breathing.

No one told me that 25 years later, I would worry every time she sleeps too late in the morning. The fear of what I might find opening her bedroom door and wondering if she had an attack, wondering if I lost her in the middle of

the night.

Throat swells and losing her is a great fear, but there's everyday pain of watching what she goes through, the emotional toll and the parts of her life that have been taken.

We almost lost her last year, not to HAE, but to an infection. She became septic from the port that she needed to be able to access the medicine. The multitude of ways that we can lose our loved ones and the many ways HAE takes part of their life from them is vast.

We're fortunate that she was able to get on to a clinical trial and it is making a huge difference in her life, but there's drugs in the pipeline that can make an even bigger difference not only for her, but for all the others.

As a mom, I don't have HAE myself. I don't know what my daughter goes through. I just know the fear of losing her and wanting to do everything possible to keep that from happening to her, to everybody in this room. Thank you.

MS. LIPSCOMB: Thank you.

MS. KLINGER: Hi. Lydia again. I just want to say first of all what you said about potential I think is something that our entire country should hear when we're debating health care and access to health care. Because while it seems like just a greater expense, it's truly an investment in our country and the people of our country.

Moving on, I would like to emphasize what my friend over here said about mental health, because I think I've seen -- I have Hereditary Angioedema, my mother has it, my brother and sister who are in their early 20s have it, my kids probably have it, thankfully no symptoms yet, and they're six and seven.

But I think that the constant anxiety of not knowing what to expect from your body impacts us probably more than all of the other lists, just because you really don't ever know what to expect. You don't know what's going to make you swell, you don't know how you're going to feel from day to day.

Yesterday I stopped at Nordstrom Rack and spent way too much money on shoes and this morning my hands swelled from carrying all of my purchases in the plastic bag. So was it worth it, yes.

But when you're in a constant state of anxiety, it impacts not just what you can do from day to day, but how you feel about other things in your life. When something else pops up that's unpredictable, you've already stacked that anxiety on top of the anxiety you have about just existing.

So I think while the disease itself can cause anxiety and probably depression as well, it's also being at that heightened state of awareness and anxiety that makes us even more prone to adding to that problem. So I think that's one of the biggest impacts in my life anyway.

MS. LIPSCOMB: Thank you. What I'd like to do though actually is go to the next question, because I think it's going to piggyback on this

and I think some of the comments you have might feed that, keeping in mind we might not have included everything that you think we should and we'll hear about that, I'm happy to say.

When you have an attack, what limitations in the activities of your daily life do you experience? Please choose all that apply and know that one of the -- that they're going to come back. I want you to think about it, mull it around a little bit.

We have a story to talk about.

MS. CHINN: So Jennifer on the web also has Hereditary Angioedema with normal C1 inhibitor, as was mentioned by a woman earlier, it took a while for her to be diagnosed and she has had many unnecessary eye surgeries because of this.

She also wanted to echo sentiments about the social impact of her disease and how it impacts her relationships in life and she can feel irritability and other symptoms like that when her attacks are coming on.

She also shared one other story about going to surgery for unnecessary eye surgery during a swelling attack and the nurse would not get her Firazyr out of her bag, because she thought she was drug seeking. So, again, similar themes running throughout everyone's experiences.

MS. LIPSCOMB: Thanks. I actually have this slide, so I'm going to read you what your choices are.

So the first choice -- so this is all that can apply. A, I cannot go to school or work; B, I cannot participate in family and social activities -- oh, it's not online.

MR. NGUYEN: What happened was the power wasn't plugged, so --

MS. LIPSCOMB: Let's do this, let's make the best use of your hands. A, who can't go to work -- when you're having an attack, what limitations do you experience, so if this happened to you before: Can't go to work or school, cannot participate in family activities, social activities, cannot participate in sports

activities?

I would raise my hand, just because I'm not very good at sports. I'm unable to care for myself, eating, dressing, pulling up our pants, as we found out, that was never talked about before.

(Indistinct chatter)

MS. LIPSCOMB: I'm able to care for my children, I feel left out. What else do we have? All of -- well, you can pick everyone.

Is there something that's not on this list?

MR. CASTALDO: Just a quick comment and I'll add something to the list. I think the sum total of all we've heard so far this morning, and these stories are so compelling, is that there is significant anxiety.

Lydia, you made the case and many others have about the significant amount of anxiety associated with HAE, that's even now. I would dare say that there's -- researchers have looked preliminarily at sort of the broad spectrum of stress associated with HAE. I think there is --

probably eventually we're going to see a link between PTSD and HAE. You can see why as you listen to the stories that we have here.

There's another piece of this that maybe somebody might want to comment and it comes up from time to time and that is that people also fear passing the gene on to their family members. As a result, some folks might be hesitant to have children and that's been something that we've heard about quite a bit in the anxiety spectrum.

MS. LIPSCOMB: Thank you.

MS. SANTEE: Just to piggyback on what Mr. Castaldo said. I'm a single mom and my first attack that I spoke about earlier -- I'm Tina again.

My son was only four, so he's 15 today. While I do suffer from anxiety and I do believe post traumatic stress probably would be a better suited diagnosis for our feelings, my son also has anxiety.

I believe some of that has come from seeing his mom, his only caregiver in and out of

the hospital and me not sometimes being able to be that stronger person for him to say, I'm okay, because I'm also scared.

It's heart breaking to see him get worried as a child when I sleep in sometimes or if my eye swells and my Firazyr is taking a little time to work, mom, do we have to go to the hospital, do we have to go, where should I go.

So that has been very hard on the family and I do believe that everyone has said that, but my son doesn't have HAE, so it affects our family if they have it or if they don't.

Again one of the things that has been somewhat of a relief to me is having a rescue medication where I can give myself Firazyr and stay home, so I don't have to find a babysitter or sometimes it requires that my dad comes from out of state and stay with me, because that trip to the hospital for treatment became intubation or overnight observation that went from one night to five nights.

So I just thank you guys for having us

here to talk about it, but again it's not just us, as the people in the back of the room, our caregivers, our family members, and even my future husband. I would like to meet him one day without being (inaudible), so please give us some medicine so I won't have so much anxiety. Thank you.

MS. WHITAKER: Diane again. I just wanted to, one, thank the FDA for this, but I want to tell you my entire biological family are all deceased, but everyone here is my swell family.

I don't think in any other rare disease, you will find a group of people that will be so supportive and so motivated to not only help each other but work with you and you work with us. I'm sure if you call on anyone in this room, we will do whatever it takes to help get solutions.

MS. LIPSCOMB: Thank you.

MR. SELSOR: I think one of the things that nobody's touched on as far as activities that people don't participate in when they've got HAE, a lot of times I think people forego other necessary medical treatment because they're afraid

that will trigger an HAE attack. One of the things I can think of specifically is dental work. I've run into all sorts of people with this disorder that they're terrified to get necessary dental work done, because they're afraid it's going to trigger a laryngeal attack.

I know personally once I started having airway events, I put off dental work to the point where I had a gigantic loose filling on one side of -- in a big molar. I would just chew on the other side of my mouth.

I had a friend say, when are you going to get it fixed? I said, well, I can chew on the left side. Well, what happens if something happens to the left side? I said, I'll eat soup.

But I know when I finally got treatment and even after that, and I knew the treatment worked well and -- even in the past, I never had dental work trigger a problem, but just making that first denial appointment afterwards to get everything taken care of, I got off the phone with the clinic and I was just shaking from, I don't

know, stress, terror, worried about what was going to happen when I actually went to get this stuff done.

Everything turned out okay, but I know a lot of people that I've talked to are in the same boat. They're terrified to get other things that are medically necessary done, because they're afraid of triggering some sort of event.

MS. NEAHRING: I just wanted to comment on the sports and activities thing. I was involved in competitive dance for almost my entire life, 16 to 17 years.

When I was diagnosed with HAE, the reason I wasn't able to partake wasn't because of swelling. I actually felt better when I was exercising, it was because my mom was like you're not going to school, you're not going to dance. My parents are both in education, so that was something that we -- I struggled to understand from them, but I get it now.

When I finally got on a treatment plan and got to college, I tried out for the dance team

at my school and I made it and practiced with them for four years -- for four months. After that, the team physician told me that I couldn't participate, because I was a liability to the university.

So I just want everyone to keep in mind that sometimes it's not the symptoms of HAE that limit participation, it's the other people in the environment that you're in.

MS. LIPSCOMB: Thank you.

MS. TUMA: Hello. My name is Stephanie and I have Type III, or the normal C1 S G inhibitor protein. No one in my family has it.

This question is very interesting: When you have an attack of Angioedema, what limitations in the activities of daily life do you experience?

What some of guys have touched upon is like it impacts your life regardless of whether you're having an attack or not. For the dental work, like yeah, I definitely put that off, like, no, I don't want to go, maybe I have a cavity, I don't know.

But things like that, scheduling different things, that all impacts you, it limits my ability to procrastinate like a normal student. I always try to get all of my assignments done as soon as I can, as soon as they're posted, so that just in case I have an attack, I'm prepared.

A lot of other things, that's just one example. But it limits your life when you have an attack or when you're not having an attack. The anxiety is real and I know a lot of you feel that way.

Any time I get a cold, the flu, it's not just your normal I have a sore throat, stuffy nose. I have all that and now it's walking pneumonia and I have throat attacks and I have everything else that goes on with that, and I know a lot of patients relate to that as well. So it definitely affects your -- all aspects of your life. Thank you.

MS. LIPSCOMB: Thank you. I think we have one more.

MS. FRENCH: One thing that none of the

patients have touched on yet, and I'm going to be a little brave here, physical intimacy is also affected.

We talk about whether it's your kidneys or your hands or whatever else, but when your partner and you and your relationship are also affected by it and you're afraid to have a relationship, relationship, with your partner for fear of swelling shut, and then that leads to a yeast infection or another trip to the doctor or possibly an awkward pap smear just because I love my husband, it's hard to put that into words and try to explain it.

In a way this disease has turned me into a liar. It was easier to say that I had been stung by something then to try to explain this or to say that maybe I had the stomach flu instead of explaining HAE or to say I had bronchitis or come up with any other thing to explain that sounded normal that other people had heard of, because we don't look sick.

If you were not having a facial swell or

if they couldn't see the swell, I didn't seem sick. So I would lie about what was happening to my body to make it okay for everyone else around me so they could deal with it. I don't know if other patients did that, but that's one of the things that goes with our disease.

Another thing I never thought I would have to face is my two year old -- well, at that point two and thank the lord she is seven, we've lived through five laryngeal attacks already. When she was two, she sat with us through training to learn how to do an IV. When your two year old says, yeah, it's red in the line we got a good one, what two year old should have to live like that. But she also realized that that red in the line, yeah, we got a good one, could save her life and when you celebrate that in her tiny little veins you got a good one.

The other thing is that you swing the pendulum. As a parent that has children with HAE, you swing in this pendulum from absolute dread of next attack. And then when they've been diagnosed

and they don't have an attack, I have a friend who lives in dread every day thinking when will the first one occur.

I've lived through the point now that I celebrated when my children did have an attack, because I knew that they knew their bodies could tell me what was happening. Now I have witnessed my child who is 13 advocating for herself in a doctor's -- in the emergency room actually and being able to stand up for herself at 13 and say, that is not my treatment. I will not take steroids. This is my treatment, and here's the telephone number for my doctor.

Then she has the wherewithal at 13 years old to say, I am not doubting you as a physician, i am doubting your knowledge of my disease. This is my treatment and you will do what my doctor says.

MS. LIPSCOMB: Thank you. It's getting close to our break for the first half. FDA panel, do you have any questions that you'd like to ask of any of the participants?

MS. CHALASANI: First off I want to thank everyone, all you who are in the room, for traveling all the way out to White Oak and sharing such personal stories. It is very valuable information. I know I speak on behalf of all my colleagues that we really do appreciate it.

We've heard from several folks about your triggers. We heard about the Nordstrom shopping spree, we also heard about hormones, the dental visits, but I think we would be interested to hear from folks if there are several other triggers that we may not have already talked about already this morning. I think I see several hands going up.

MS. THOMPSON: So one of the other things that's a trigger for -- I've seen in a lot of people is anxiety or stress creates this big whole runaround that never ends. The other one that I have found for myself is the change of weather. If the barometric pressure changes, I swell and I'm in bed. I'm down for the count, I can't get out, I have no energy.

When we did a summit in Denver a lot of us were swelling and having difficulties, because the barometric pressure was different than the other 49 states, so those are two that I know of.

MS. BOMAR: Hello. Someone had mentioned about pap smears -- I'm sorry, my name is Fran Bomar from Alpharetta, Georgia. I'm not embarrassed to have that on the web.

We talked about having pap smear and that is -- it's traumatic just to think about it. But unless the physician is skilled, you can leave and know that you're going to have an attack. The other is a mammogram, better known as the breast press, because it is so painful.

My husband, Ken, had asked me one time what was so bad about a mammogram. When I explained to him, it a whole different matter. So I have had an attack from having a mammogram. When your chest swells up, that's not a good thing and you can't breathe.

So those are the kinds of things, along with everything everybody else has said about

anxiety and even having commitments. I'm long retired. At this point, people say, well, why don't you volunteer for this and volunteer for that, I don't want to do it, because they can't count on me, even though I'm on treatment and I have -- I do have breakthrough attacks. Sometimes I'm just not in the mood to do it, I just don't have the energy to do it.

So there are other factors out there too, so I agree with everybody else. Yes, I'm missing parts as well, appendix and other things that people decided to take, because they didn't know what was going on. So thank you very much.

MS. LIPSCOMB: So we'll let Lonny's person go first.

MS. BRAHEN: My name is Peggy. It's not just stress and anxiety, but it's any -- it can also be happy things, like you're so excited about something, you're surprised about something, it's emotions.

If I'm really happy about something or if I'm really mad about something, it can -- they

used to call it Angioneurotic Hereditary Angioedema, because it was all in your mind and that's -- a lot of people they have -- and it is. This disease is bridge between Western and Eastern Medicine in a way. The mind can very much affect the physical symptoms.

I don't think sometimes the drug companies and everything get that it's -- when we smile, there's chemicals that go on that do things. So it's just not stress and anxiety, which are a great part, but it's also the opposite spectrum too.

MS. PERRY: Louis Perry; Fresno, California. One of the things to remember too growing up I had this same problem, everybody would ask why did you swell. Sometimes we don't know.

The fact that I don't have enough working or functional C1 inhibitor is enough to make me swell. A lot of times I have no idea, and that was part of the stigma. Especially since my dad died so young, my mom always wanted to know

what happened, what happened. You don't always have an answer, but you swell.

MS. LIPSCOMB: Thank you. We're going to take about two more, because then -- it's 11:31 now.

MS. BEITER: One of the things that I definitely wanted to touch on was I know for me infection is a huge trigger. The second I get any type of -- even viral or anything, it triggers something to happen.

That was actually how I was diagnosed. When I was in my senior year of high school, I was homeschooled for six months because I had a sinus infection. To tell someone you're homeschooled because you have a sinus infection, you sound absolutely awful. It's just -- you sound like a baby.

Every time I would -- the infection would flare up, my face would swell. Then the doctors thought it was such a bad infection that they started doing swelling, because they thought the swelling was from the infection.

A lot of times I know that the triggers sound simple, but it can create an awful cycle of like hormones and then you end up stressed, because you don't feel well and then you swell and then you're stressed because you're swelled.

I think a lot of us get in a pattern of infections and then doctors trying to treat it with medications. I know there's some people that have problems with certain antibiotics that cause -- is a trigger.

Like she said sometimes people are like, well, why did you swell? You're like, I don't know, maybe because the sky's blue. You really can't explain what is going on in your body, because it just happens when it wants to.

MS. LIPSCOMB: Thank you.

MS. KLINGER: Hi, Lydia again. Just to kind of clarify on the Nordstrom shopping trip, what that trigger was is soft tissue trauma. Which was not a large trauma, but any little thing for me, like to my body, that is traumatic to my soft tissue can make me swell.

For example, I don't know how many people with small children have ever been face bopped by your kid coming up when you're going down to kiss them, I've had numerous facial swells because of that, just getting little tiny conks in the face from my kids.

If I am gardening or something, if I'm pulling weeds for too long, that always makes my hands swell. Holding a rake is not possible. I can hold it, but there's no raking. My husband still thinks I'm just trying to get out of something.

But dental -- oral surgery is a huge trigger for me, when I was in college just always around exam time I would swell from that emotional stress. After college I thought that I needed to have two full-time jobs, and that was a bad idea, that caused swells, basically the fatigue. So it can be any number of things.

MS. LIPSCOMB: We're going to have one more and then we're going to cut.

MS. CONKLIN: Hi, I'm Katie. One of the

things that can happen is just repetitive motion, so just walking, and usually I can control it by wearing sneakers. I've gotten to where even if I know I'm going to be doing a lot of walking wearing sneakers, within a couple of hours I can start an attack, whether in my feet or in my knees or in my hip just from the repetitive motion of walking.

MS. LIPSCOMB: Thank you, everybody. I know there's so much more -- so many more triggers that we could hear -- okay. Ross, go ahead. No lunch for you.

DR. PIERCE: Along the lines of repetitive motion, one of the web participants mentioned if they were driving a car over a road that had been resurfaced where it was graded.

Also one participant mentioned textures of food and also things that are very salty or acidic foods like tomatoes or vinegar based.

MS. LIPSCOMB: Thank you. I feel like we covered so much. I hope I didn't cut off any of you guys; right. We're going to ask for you to

come back at what was going to be 12:30, but I'll give you to 12:34. We're going to start right on time. In the afternoon, we're going to hear about your perspectives on treatment and clinical trials.

I think we'll probably continue the line like what we've been talking about. Again, thank everybody on the panel so much for sharing your experiences. Thank you for being so willing to share. We are so thankful.

I don't promise that lunch isn't great, but I love it, so that's all I'm saying. That might say more about me than you. We'll see you in about an hour.

(Recess)

MS. LIPSCOMB: I, once again, would like to direct your attention to the FDA panel. We have a couple of new people sitting on the panel. I'm going to go ahead and let you and Stacy introduce yourselves.

MS. CHINN: Hi, I'm Stacy Chinn, I'm an allergist, immunologist in the Office of New Drugs

in the Center for Drug Evaluation and Research.

MS. MUELLER: I'm Christine Mueller from the Office of Product Development.

MS. EGGERS: I'm Sara Eggers from CBER's Office of Strategic Programs.

Dr. PUROHIT-SHETH: I'm Tejashri Purohit-Sheth, division director for Division of Clinical Evaluation in pharm talks in OTAT CBER.

MS. MALONEY: Hi, I'm Diane Maloney, associate director for policy in CBER.

Dr. GOLDSMITH: Jonathan Goldsmith. I'm the associate director of the (inaudible) program in the Office of New Drugs, CBER.

MS. LIPSCOMB: Thank you. Thanks everybody for getting back. I hope you got your lunches without any kind of hiccups. It seemed to be going pretty smoothly. This afternoon, the first topic is about current approaches to treatment. I'm going to invite our panelists, Joyce, Janet, Karen and Anthony to come up please. What we've asked this time for discussion, and we'll leave this up so everyone can see it is,

what treatments are you currently using, how well do the treatments work, what are the most significant advantages and disadvantages, complications of the treatments, how has your treatment regimen changed over time and why. We heard a little bit about that earlier. What aspects of your condition are not improved by your current regimen and what treatment has the most positive impact on your quality of life. As we found this morning, if somehow these questions need to be tweaked by you, we certainly understand. I'm going to go ahead and invite you to start speaking and we'll go down this way please. Make sure you put your mouth close to it.

MS. PERRY: My name is Lois Perry and I'm grateful to be here and have the opportunity to talk in front of the FDA about hereditary angioedema and the current approaches to treatment. Not a lot was known about HAE in my early lifetime. Over the years, I was relegated to medieval HAE treatments that simply didn't work. I'm fortunate during a bad throat attack, a

doctor at my local hospital had heard about the NIH and their studies that they were doing and suggested that I went to NIH. That was in 1976 and that was the start of my journey. Finally, in participating in HAE clinical trials in the search for a better life. I participated in the first clinical trial at the age of 17 at NIH. I've been in two clinical trials since then which were targeted directly towards being able to allow patients to live a normal life by treating and replacing the missing protein in my blood. Clinical trials aren't easy, it is a double blind placebo portion which means you have to go off your medicine and go on a placebo and suffer attacks. I was allowed rescue therapies for the trials but just knowing I had to give up a therapy that worked well for me to try to find something better had a significant emotion toll during the trials.

For me, the clinical trial site is a 3 hour drive one way so it is a challenge but it is well worth it. I treat every attack regardless of

location due to not knowing when those attacks can move from hand to stomach to face to throat. I currently use a sub q version of the C1 inhibitor. The current treatment has changed my life drastically. Back in the day when I was first diagnosed, all there was, was nothing at first and then Danazol, Stanizol, Oxzandrin. Going on those therapies for 30 years, I had a heart attack when I was 45 years old. While they did keep my alive and I am grateful to having had those therapies, it's not optimum. So, I'm really happy to see the therapies that we do have now. I've witnesses many milestones living at a young age with no therapy and being sick constantly in and out of the hospital, missing school, work, activities just like everyone said. Of course, I'm 59 years old, I admit that, and therapy has been only approved since 2008. So, there were many, many dark days that I had been prescribed everything that they ever thought would be working for swelling. Today's modern therapies are wonderful and life changing as you have heard already many

times today. But I still have to remember not to miss a dose and I'm always aware of any little thing that used to bring on an attack. All my attacks are well controlled now, it's always in the back of my mind that I could have an attack anytime, anywhere. So, I have to always remember to take my therapy wherever I am. It's very critical to have that care plan in place.

In a perfect world, longer lasting therapies would help me live as if I didn't have HAE at all. The therapy that could soon ward off attacks for longs periods of time would allow me to almost forget that I have HAE. Therapies even with easier methods of administration are something that I am greatly looking forward to and hopeful to see progress in my lifetime. Would I do clinical trials again, of course. Because one day I hope to live in a time when HAE is something that I have that doesn't have me.

MS. WILMOT: My name is Joyce Wilmot and I have HAE type 1. I started having recurring stomach attacks when I was in the early 1990s

while I was at college. Everyone attributed the stomach issues to ulcers, college stress, stomach flu's et cetera. I was getting frustrated since no one was able to figure out what was wrong. Coincidentally, my older sister who was in medical school at the time, also started having similar symptoms. So, she dug into her medical books and was able to come up with a diagnosis for both of us. So, in that way, I was very lucky that it took a little less than a year to get a diagnosis. After I finished college, I pretty much limped along. I was fortunate that I only had 50 to 10 attacks a year, most years I was able to limp along. Any time I had an attack, I would lose three to four days out of work, out of life, in and out of the hospitals. I remember those days curled up on my bed waiting for an attack to end. I participated when the clinical trials came around, starting with the Baxter. I was participating in the trial. I remember I was pregnant with my twin girls when the Baxter trial was going on. There was one point where the trial

was discontinued and I remember in my bedroom just crying because the trial was pretty much keeping my babies healthy at that point because I was getting an attack almost every week while I was pregnant. When the clinical trials came around, I participated pretty much in all the ones I could. Currently, I am not on prophylaxis. I have rescue medicines. My doctor started me on Berinert when it was approved. That takes care of my attacks pretty well as long as I take it early during the attack. If I take it too late, I would still have to deal with the residual swelling for another day or two. For the most part, that works really well but I soon realized that I needed something else. I was in the middle of a camping trip with my daughters for a girl scout troop in the middle of nowhere and I had a full blown attack. I realized I had no access to clean water, antibacterial soap or any kind of clean surface to do my prepping for an infusion. It was at that point that I realized I probably needed something else. So, when Firazyr was approved, I spoke to my doctor and we

added that to our tool box of how to handle my HAE attacks.

So, unfortunately, the HAE meds work differently for all of us. Firazyr for me will stop the attacks pretty quickly, the progression of the attacks but there are times when I would get a rebound attack the day after. So, even though it is a lot more convenient then my Berinert at the time, I still have to rely on a C1 inhibitor some of the time to fully get rid of the attack. So, I'm just thankful these days that the physicians have several medications to choose from because the treatment plan has to be customized for each individual.

My daughter, who just turned 15, has recently started getting abdominal swells. So, I have learned to infuse her. She's someone who is awfully terrified of needles. When she was six, she would hide under a chair to keep the doctors from giving her her shots. So, it's been a challenge for her. I'm looking forward to the day when there is a treatment that is easier to

administer. I remember a couple of months ago, she had an attack. She was dehydrated at the time so I had a hard time finding a vein to do the infusion. I tried three or four times, I still couldn't get one and so I started calling urgent cares and emergency rooms hoping that I would get quick help in infusing her. It was then that I realized that we still have a long way in educating doctors and emergency rooms as how to treat HAE. The two or three urgent cares near our house pretty much refused our request for help. They said I couldn't bring the medication in. They just didn't feel comfortable giving her the medication. I called a couple of emergency rooms and I wasn't getting a definite answer whether they would do it or not. Thankfully that night, I was able to infuse her and everything was okay but I still have concerns over the next time she has an attack and I can't get vein access for her.

I just want to stress the idea that we still do need better medications. Our pharmacy ships two doses at a time for us. I'm just

fearful that a disruption in the supply line will take the medications away from us. I cannot imagine going back to the dark ages when we don't have medicine. I'm just thankful for this opportunity to air our concerns and hopefully the FDA will see the need to keep the funds going in to HAE research. Thank you.

MS. LONG: Hi, my name is Janet Long. I'm also very grateful to the FDA for this opportunity to speak with you today. My story is not very unsimilar from those you've heard but it illustrates life without therapy so that's where I'd like to start. I was 7 when I experienced my first HAE attacks as far as I can remember. To this day, I'm haunted by the look of helplessness on my mother's face when she could only offer me a hot water bottle and a couple of baby aspirin. Treatment, we both knew, would do nothing to ease my suffering. As a teenager, each monthly period meant excruciating pain and days missed from school due to severe HAE abdominal attacks. Sleep overs with girlfriends meant a constant worry that

I would need to call my mom to take me home because I was the one too sick to be a normal teenage girl at a sleepover. At 21, I experienced an abdominal attack so severe it caused internal bleeding and I underwent an unnecessary exploratory laparotomy and spent a week in the ICU. Despite the innumerable tests I went through, no one could figure out what was wrong with me and the ensuing years brought nothing but scores and scores of doctors who either admitted to being totally baffled or offered theories from sinus drainage to chronic colitis. I knew none of these guesses were the answer.

Over the years, I continued to suffer mainly abdominal attacks. I was tired of showing up at the ER only to be sent home. Every physician told me nothing could be done for me and I would just have to learn to live with the pain. I vividly remember my first throat attack. My general practitioner had told me it was all in my head and that I was imagining my throat closing so I took two Advil and went to sleep and by all

rights, I should not be here today. I should have died that night except for a spontaneous remitting of the swelling. My abdominal attacks used to last for three days but with some time in between attacks. With hormone replacement therapy, my attacks started to come one right after the other. Three days of nausea, vomiting and diarrhea followed by three more and three more and three more. The toll on my body was so unbearable, I was convinced I was going to die. I faced what I believe was the very real possibility that my three beautiful young daughters would be left motherless. I told my husband, if I don't make it through the night one night, please tell the girls that I love them.

After 40 years of suffering, a brilliant gastroenterologist unraveled the mystery of my life and diagnosed me with HAE. I know she saved my life because throat attacks are coming once a week and one would surely have killed me. One of my three daughters inherited HAE for me. She was fortunate to be able to participate in clinical

trials in middle and high school. She suffered tongue and throat attacks which is not surprising in the teen years when stress is high and we know that HAE is exacerbated by stress. Without access to clinical trials, she would have died on more than one occasion. I am so grateful for the trials for all of the now FDA approved therapies.

Today, my own HAE attacks are so severe and frequent, that I need prophylactic therapy but I keep an acute medicine with me at all times, according to the HAE's medical advisory board guidelines. This just makes good sense with a disease that is so unpredictable. Not all therapies work for all patients or even in the same way during all periods of your life. We are so fortunate to have more than one choice to treat HAE attacks.

FDA approved treatments meant I had an alternative to attenuated androgens and their debilitating side effects which were my only option when diagnosed 18 years ago. My HAE physician and I agree that it is important to make

my therapy choices according to my needs and to live a normal life. I'm grateful for the HAE experts that we have working alongside us who have also made possible these FDA approved medicines.

My grandmother had HAE though no one knew it. Of course, in those long ago days, near the end of her life in the late 1970's, doctors did not know what to do about the pain and swelling in her face. So, they cut all the nerves in her face. Current and newly developed HAE therapies mean we've come a long way but we still have a long way to go. I hope that my daughter will never have to suffer as I did. Of course, the ultimate goal is a cure or a treatment that is in essence, a cure. But there is not a day that goes by that I am not more than thankful to still be alive, to see the advances in HAE drug development already achieved and still to come. Thank you so much.

MS. BAIRD: My name is Karen Baird and I reside in Houston, Texas. I also want to thank the FDA, the panel that's here today, so much for

your time. I want to thank Donna Lipscomb, you're just a joy, your sense of humor. I called you the comic relief in the hallway but you're so compassionate too and it is just such a pleasure to be here today. When I talked to Donna on the phone, we discussed a little bit and she wanted me to share about the mother's heart. I feel that that's really the caregivers heart, not just a mother's. I want, for just a moment today, to talk to you about the mother's heart, the caregivers heart but also the perspective so we don't get off track on the therapies that my children are using.

I have two children who suffer with HAE. My son, Kyle, showed his first symptoms at age 2 and he is now 33. My daughter, Ava, showed her first symptoms at age 15 and she's now 29. My husband, Sandy, is the carrier of HAE. He's 58 and has only swelled two times in his life which occurred in his 40s. I feel he is sort of a marvel. I've spent the past

years pleading the cause of my children.

I became my sons mother in 1984 and I became his caregiver in 1986. HAE has affected every aspect of his physical life as Kyle has an attack every four days. The first 17 years of his life were filled with attacks, pain in his body, tears and anxiety with no treatment. Of course, as a mother this caused tears, pain and anxiety in my heart. I felt that I was groping blindly in the dark. I was reaching out for anything I could touch to find any kind of stability of our family, all the while knowing that the worse could happen and that would be a laryngeal swell.

As with all of us, I could not find a physician that could help me, that could explain to me or how to even treat it. Our family history, there is 50 percent of us in the Baird family that have this disease and they all knew very little about it. So, for over the past four generations that we can count back to my son Kyle appears to have the most extreme battle with HAE. He seems to carry the greatest burden. It has affected his daily activities through all the

chapters of his life. Attendance in school from elementary to graduate school, participation in sports, family vacations, holidays, birthdays. Someone mentioned earlier about just the excitement. I can remember every birthday, my son spent his entire time in the bathroom with diarrhea, even as a little boy, to where he didn't want to have a birthday because he associated his birthday with being sick. All it was, was he was just excited about his birthday party. It was very sad. And then going on to college, all of us know, the dorm life, the dating. My family, we work in Africa and our children work with us so that was an added difficulty for us of leaving the borders of the country with both of my children having this disease.

My son is a professional now. He's a history teacher, a football coach but he's now at a place in life where his wife is the one working and he's the stay at home dad because it really is the right thing for him right now because he struggles so much even with therapy. He just

generally feels ill all the time. So, despite his fortitude and his graciousness in having this disease and his faith and hope, he struggles on a daily basis.

We're so grateful for the day that we were introduced to HAEA. So grateful to Tony Castaldo, so grateful to so many people that really have changed our lives that we feel that we're part of something. After Kyle was about 17, he started on Stanazalol, an androgen and after five years on that, he started having heart palpitations. He made the choice to take himself off of it which was a very dark day for me because for five years I really felt that I could have a little bit of breathing space. I knew that the androgen was helping him and as a mom, I just took a big deep sigh. So, the day he went off of it, it was terrible for me to say, no Kyle don't do that, I want you to stay on it. I knew he didn't need to be on it but I wanted him on it. He went off of it and his swelling began again.

In 2011, Kyle began to infuse with

Berinert and it worked very, very well for him. And then he went, because of insurance purposes, he switched from that to Cinryze and it has worked well but not as well from his testimonial to it as Berinert. As we all know now that the production of Cinryze seems to have taken a temporary halt, hopefully -- Kyle found himself last week with nothing. Once again for himself, our family and myself as his caregiver even at 33, that dark cloud comes back over me because I realize that my son, once again, needs help. Ruconest has come to the front for us in a very quick and timely fashion and now he will be starting on Ruconest this week. So, we're very excited and grateful for that.

In 2003, my daughter Ava at age 15, had spent the weekend surfing. On Monday, when I picked her up from school, her hand was swollen. I think that was one of the most difficult days of my life back then because I drove back in the car trying to have a smile on my face, realizing that 15 years into her life, it never occurred to me

that Ava would have it as well. And then to realize that both of my children have it. So, I found myself as a caregiver in a position that all my people have it, everyone in my house.

Since 2004, I've worked in 35 countries rescuing children. Tony and I had had a meeting with Tom Delay. I remember sitting there telling Congressman Delay is that one of the most disheartening things in my life as a mother is to come back to the United States and not even be able to rescue my own children. Again, there was a bright light as Ava began therapy treatment with Berinert in 2011. The quality of her life has greatly improved. Ava is different from Kyle in the sense that she swells three to four times a year but it is always laryngeal. So, for me, I consider her to be the more extreme of the two of my children.

One would look at my children and see two beautiful adults now who appear to be completely healthy. They are both married, they're parents, they're productive, they work all over

the world. Their therapies have changed their lives. Their therapies have given them security and given them freedom and we're so grateful. But I go back in my mind to Christmas 2016. My family was gathered at my table for dinner, it was Christmas Day and Kyle was sitting beside me and he began to act strange saying that he felt his food wasn't going down the right way. Within seconds, Kyle collapsed over on me. And at that moment, as reality soaked in, I thought it's Christmas Day and I've lost my son. He was swelling and we were immediately able to infuse him with Cinryze which saved his life. I remember my two year old grandson Beckket crawling up on his daddy's chest and crying, even at two. He knew enough to know that something was really wrong with his daddy. Needless to say, it was really hard that night to carry on and open all of our gifts with the sobering reminder of this disease and how quickly it can change our lives. That night when I went to bed, here's what I thought. I thought to myself, if Kyle dies from

HAE, he'll be in heaven and there will be no more suffering and that seemed to be my comfort.

Now I realize in my children's lifetime that there really could be a cure with the timeless research of our physicians, our scientists, the vision of a cure has begun to appear on the horizon within our region. I'm beginning to realize that HAE could actually be a memory in my children's life. It would be something in their past and not something in their future. So, I'm not ready for my children to go to heaven so that their suffering can end. I'm ready for my children to have their heaven on earth.

MR. COSTALDO: Good afternoon, I'm Tony Castaldo. My HAE story is kind of boring. I was diagnosed at the NIH a long time ago. I'm one of these people that actually did really well on androgens. I could get a relatively low dose of androgens and have some breakthrough attacks but pretty much my story is very boring. 35 years on androgens, I tell everybody that all of this is

because of androgens, my doctor says no, you eat too much. We'll go with whatever the story might be. I would like to share the sentiments of the panel here and thank the FDA for conducting this patient focused drug development meeting. I think this really does show that the Agency has a commitment to hearing the patient's voice and hopefully we'll see that translated into the regulatory decisions as well. I'm also very happy that we have somebody from CDER here. You'll be having a bunch of products up for review, I think you have one now and we would like to make sure that the message here from the patient gets percolated throughout the division. Hopefully Dr. Chowdhury will get a chance to look at the transcript as well and we're glad everybody is here today.

So, being that my story is boring, what wasn't boring, however, was that of my daughter. Age 5, weekly abdominal attacks, horrific. Covered with erythema marginatum which is the rash about 25 percent of us get. This was a really,

really sick kid. We had an intractable situation with her and fast forward, we worked really hard to try to figure out a solution for this beautiful young child. Three days a week at Georgetown Hematology. We were frequent flyers there for fresh frozen plasma which really kind of worked but I'm not quite sure. I'm a compassionate dad, I have the disease. I'll never forget one time on the way to Georgetown, my daughter looked at me and said, dad all I ever really wanted was just to go to school. I'm a perennial C student and I said what, but then I got it. This was a kid who wasn't going to give up, all she really ever wanted to do was live a normal life and she looked at me and said can you help me. That's where it began.

That's where the advocacy you see in front of us today. We have here in this audience, some incredible patient advocates. People who have given up their day to come here all to be part of a cause and that's the HAE cause. We've heard the stories today from each on the

individuals, each one of these advocates here today. The passion and their concerns for themselves, for their children and amongst all of that is their children's children as well. So, I just wanted to give you guys a hand for being here today. Thank you, HAE advocates, for your participation. You make a difference. Why do you make a difference, well think about the dark days and everybody has talked about the dark days. Some of you might remember that we had a program back before had access to medicines where we actually imported medicines from overseas sources and the Agency was actually very helpful and the enabled us to do a program where we would bring the medicines in and we met certain provisions. Mary Marlarkey at the time, was the head of compliance, and that program saved a lot of lives.

But that motivated us further as a patient community to get organized, to work together. We've heard testimonials today of how that's worked. Well, that has resulted in something really special at this juncture. There

are many other disease states out there that don't have the kind of advocates that are sitting in this room today. Don't have the kind of physicians that are also sitting in this room today and also the cooperation from the pharmaceutical companies. HAE now has six approved products to treat the disease. That is quite extraordinary given the limited size. Why did that happen? That has happened because of the people sitting in this room. We have a galvanized patient community and we'll talk about this a little later when we talk about clinical trials. There has never been an instant where HAE patients haven't been willing to participate in clinical trials and some of them are pretty difficult, quite frankly, a require a big commitment. But this community, the united and galvanized community has never blanched from taking it on the chin and participating in clinical trials.

We also have an incredible cadre of physician researchers, quite unique for a disease state like ours given that this really an

ultra-orphan rare disease and some of them are here today. They work selflessly, they care about the patients and they understand the disease, they understand the devastation that we've all heard about today about what this can do to people's lives. And these physicians have been willing to participate in clinical trials, participate in patient care, participate in research and do the things that are necessary and that's part of it.

And then we also have had industry and I think we've all forged a great relationship. I think we've forged an excellent relationship with industry and thank goodness for their investment in these products and that's where we are today. However, and this is a huge however, ladies and gentlemen, I'm here to tell you that the game is not over by any means. The game is not over by any means. Dr. Pierce, who've I'd have the pleasure of interacting with in the past, who has been a CBER reviewer and knows the disease quite well, he said something very key this morning when he made his talk talking about Hereditary

Angioedema. He said, no proved therapy eliminates all attacks. Think about that for a second. So really, where are we right now. Yes, we finally through the grace and goodness of this community, the physicians, the patients, pharmaceutical companies working together to get things done, we now have products where lives have been transformed.

But if you look at some of the studies that we do, we're not quite there yet. I'll just give you a couple of quick statistics. We actually did a quick study of 980 patients not too long ago. If anybody wants to think that the game is over for HAE, listen to just a snippet of some of these stats. 74 percent of the patients that we polled in our 980 patient sample said they had more than one attack a month.

percent of that sample said they had more than one ER visit in the preceding six months. 50 percent said that they were somewhat to not at all satisfied with their available therapy. Basically, we also found that 50 percent

of the patients we polled either had used or were currently using and indwelling port.

So, that's the message here today. We've heard about the stories. We've heard even with therapy there is still a high level of anxiety among patients. There is still a fear that one day we might not wake up. So, I think it's really important that the agency hears these messages and when products come in front of you for review, it's important that you understand that there can't be any complacency. Obviously, as regulators, you are entrusted first to protect the public health and safety, I think we all agree with that. We think that's paramount, paramount importance. However, within the confines of that, we would just ask you to work closely with industry, with expert physicians who can come in and speak to you about what is going on because we still need and have a need for better therapies and ultimately a cure. Thank you.

MS. LIPSCOMB: Well thank you to all of our panel, thank you very much. How many of you

in those conversations recognize your treatment stories? Does anybody want to talk specifically about any particular treatment? Let's go and do our next question please. So, which of the following medications do you currently take to prevent an attack? I would then to read these but then you would have reason to laugh at me. We're going to read this one. Well, we're going to go back to hand raising. I know for some of you, if you're using them, raise your hand for each and every one that we're doing. How many of you are using, A is Danazol or a similar steroid based medication. B is Cinryze, C Haegarda, D other, E I do not take any medications. Let's vote. That seems to track like your hand raising. I'm glad you weren't telling me stories. So, what about medicines -- Ross what was the web like?

MR. PIERCE: So, like in the audience here, the most popular answer was other and that was twice as frequent as collectively, Cinryze and Haegarda which were the other popular choices. There was only one participant from the web who

was taking Danazol and everybody was taking something, nobody chose choice E.

MS. LIPSCOMB: Okay. What about, let's talk about medicines that are used for treatments and attacks? Chris, can you hit the next one. Which medications do you receive from your healthcare provider to treat acute attacks and pick all that apply. I think we heard a couple of you talk about how helpful Firazyr has been. We're going to ask one more medication question and then I'm going to let you guys have a chance to talk to me about it. Chris, I'll check with you guys about the web. How was twelve?

MR. PIERCE: Firazyr Icatibant was the most popular choice followed by Ruconest and Kalbitor, Berinert was after that.

MS. LIPSCOMB: Okay, so very similar. Let's talk about the medications you're using on the results. Especially for people who wrote other in this one, what are those treatments that you use?

MS. YODER: I think I already mentioned

earlier that I was on the Danazol for 33 years and just got off of it three months ago and started on the Berinert because of the cholesterol issues. It's a prophylactic now. I started that, I did have it for catastrophic attack but now I'm taking it as a prophylactic.

MS. LIPSCOMB: Okay thank you. Anybody else?

MS. BRAHEN-GRESSENBACK: Yes, I was on from 1974 until 2011 I was on Danazol and I actually switched from Danazol for the last five years to Oxandrolone because it was less affecting me because it is less masculinization. And then I hit menopause and the Oxandrolone was messing me up so I went off that and I had 53 attacks in one year. In 2011, I found HAEA and met a doctor and he mentioned Firazyr for me because that was available. I started using that, it cut down my attacks from 53 to about 25 the next year. But then I was starting to have rebound attacks. So, then I went on Cinryze and I was on Cinryze but then I started again menopause having hot flashes

so I went on a real low, low, low dose 0.25 of bioidentical estrogen because hot flashes every 15 minutes, the quality of life, I don't care if you have angioedema or not, you have to balance quality of life with everything else happening. So, the Cinryze I was breaking through a little bit and then it became unavailable in 2016. So, in 2016 I switched to Berinert and then that's weight based and I haven't had any problems except for real excitement or something with breakthroughs and then I use Firazyr and then I follow up after Firazyr with Berinert because of the 24 hour rebound that I have. So, I guess I'm of all these therapies that are available, I'm almost used all of them. As life changes, as your experience changes, for women especially who have hormonal changes, you have to switch and use different things. Also, in this case, it's just not the hormones it is actually companies. When the companies change and they can't provide the drug, there has to be something else out there that we can go to. Because if I didn't have, I was

in a clinical trial for subcutaneous and I got the saline unfortunately and I started attacking every two or three days and so I had to actually drop out of this particular clinical trial because it was too dangerous for me. So, I guess what I'm saying you have to have different drugs to go back and forth to.

MS. LIPSCOMB: Thank you. Did anybody else have other meds you wanted to mention?

DR. BUSSEY: I wasn't going to mention about the treatments, I'm a physician. My name is Paula Bussey and I take care of a large group of patients with HAE and I just want to talk on the physician's side. It's wonderful now to be able to provide patients with medications but yet there are several frustrations that we have and I would like you to be aware of them. One, there is a lot of paperwork that's involved in making the prescriptions and sometimes very frustrating things. For example, if I have had patients that haven't had their medicines filled because for example, they have to prove they have HAE. I have

bloodwork from several years ago that proves they have HAE but I'll get calls back from the insurance company saying, I need recent blood work. Well, this is a genetic disease, it doesn't change. So, patients that have a lapse in their therapy which is not good and extremely frustrating for myself.

Another thing I think is important for physicians and everyone to be aware of is the proper use of the medications and the proper prescription patterns. Make sure that the patient really has HAE or has hereditary angioedema because with the shortages that we do have sometimes, when medications are not prescribed properly, the patients who need it may not have it. Those are some of my frustrations.

MS. LIPSCOMB: Thank you.

MS. EDWARDS: I'm Carol. Before I was diagnosed with HAE, I started taking testosterone for libido which worked very nicely. But I noticed that same week, I was getting an HAE on my way to work and it was like half as bad and I was

like hey, just give me a couple of hours, I can continue on with work. That was the first time since I was 10 years old that there was any deviation into an attack not being as bad. When I was diagnosed with HAE probably about six months later, my HAE doctor actually prescribed a testosterone for me for another six months because my attacks were so much less severe. That was the other thing I used and it helped me. I'm not on it anymore. My husband enjoyed it but I couldn't take it anymore.

MS. LIPSCOMB: Let me ask the next question real quick.

MS. LONG: I just wanted to mention, a lot of women have mentioned the role of hormones. Progesterone only therapy can also be used sometimes. My daughter chose that route when there was no therapy currently approved by FDA and it works for her. It doesn't work for everyone to our point that not everything works for everyone. But sometimes progesterone only can be affective for HAE.

MS. LIPSCOMB: Thank you for adding that. We've heard in our conversation that when an attack is coming, you or your caregiver at home administer treatment. So, different people may feel different symptoms as harbingers of an upcoming attack. Our next polling question is about when you feel a treatment is needed. I think a couple of you have talked about that. A, no symptoms appear but you can feel attack coming on. Once symptoms interfere with activity, once pain or discomfort from swelling becomes intolerable. That seems to be the most, C and A. What about the web?

MS. BOUCHKOUJ: Similar responses, C and A.

MS. LIPSCOMB: Okay thank you. We would appreciate if some of you could share your experiences about this phase.

MS. STARR: For me over the years, I've learned that effective treatment is to get it right away when the attack starts. I've learned my prodromes like symptoms that start before an

actual attack starts is when I treat. Because if I don't, then I'm already in pain, the swelling has already started and it takes longer to resolve. So, I've learned how to do it that way.

MS. LIPSCOMB: Thank you.

MR. CASTALDO: So, just to comment here about this data here is quite remarkable and not in a good context, quite frankly. Because I invite anybody who is a non patient to think about how you would feel if you had to get sick to the point where pain and discomfort becomes intolerable before you could treat. That's not an acceptable way to look at it. Now, recognizing there are certain situations where you can't get to the treatment soon enough. This is something that I think our medical advisors have always stressed and it is so important that for those patients that are on, on demand therapy, the earlier you treat the better. Because you can stop whatever is going on biochemically that is causing the swelling. You can stop that pretty quick with the available treatments. If you don't stop it and you

let the swelling get into your tissues, you are sick and then it is up to your body to reabsorb those fluids and you'll be sick until it does that.

And let me just make one other point that I think is very clear as we've talked about the array of acute therapies that we have available for us. It is very important that everyone understands, there is variability in effect and we hear this a lot from our patient community. There was a lot of variability in how various therapies work for various patients. Those were valid concerns. One of the things we're blessed with at this juncture is that we have therapeutic options. That's a good thing because what we find on that is that not everything works for everybody in the same way.

MS. URBONIUKI: I want to say as a patient, it's really important to treat early as all of us know to just shut that pathway down. You're going to feel a lot better sooner. In talking to some patients, I've heard before, well

I'm just going to deal with it if it's like an attack on my hand or my foot. I'm not sure how a lot of people are but I know for me it's never just my hand. And you never know, it could travel to various places, abdominal, even laryngeal. It's just really important to treat every attack as soon as possible.

MS. LIPSCOMB: Thank you.

MS. EDWARDS: For me, I need an F on there because I have to wait for my symptoms to appear but I cannot take them until they are intolerable. As soon as they appear and I'm sure it's an attack, I want to treat right then but my symptoms have to appear otherwise I don't know it's an attack.

MS. CLASEN: Hello, I'm Liz, again. I think there is two sides of the coin for many of us who have gone so long without diagnosis. One of the positives is I know those warning symptoms, I know them really well because I suffered for so long and I learned my body so well. The flip side of that is you begin to think suffering is

supposed to be part of your life, so I had this weird human psychology around, oh it's just a hand attack and this is my lot in life. So, I really want to say a huge thanks to HAEA because I think very loudly and frequently say, treat attacks early because it is more effective and treat every attack because it is your right. It's your right and we have that benefit because we have these therapies not to have to suffer. There is still this weird human psychology that it's important that my husband and that my dad has heard that so they can remind me when I have an attack like, oh yeah I should do this, because sometimes I need that extra voice because suffering had become so my normal.

MS. BREADY: I was always told from my doctors, because I take an acute therapy, that is I would have swelling in my face or my throat or stomach, to take the medication right away but not to take it for my hands or my feet. So, I'm just like recently like I just deal with a foot or a hand swell. It is very interruptive and I think

I'm going to start taking for my hands and feet. I just wanted to make a comment too on some of the questions here. Sometimes I'll wake up in the middle of the night too with a throat swell. It's not like I'm thinking, oh I'm starting to feel, you're sleeping and you're waking up at 3 in the morning and your face is swelling or your throat is swelling and you're like, oh no is this real and then you treat.

MS. LIPSCOMB: Thanks, we're going to take two more.

MS. CONKLIN: I want to speak to what Liz said. My name is Katie. So, you say to treat when you start to have an attack and I know from experience. If I start to have an attack, if I take that medication immediately, I feel better and that usually stops the attack. However, with the shortage of medication most recently, my last dose of Cinryze was on September 10th. Three days later, I began to have attacks. I had an attack for 11 days. I'm lucky that I had Firazyr on hand. However, Firazyr did not stop the attack.

I ran out of Firazyr and it was a battle to get Firazyr. So, I'm always hesitant to treat a hand or a foot attack when I am low on medication because what if I had that laryngeal attack and by goodness, I'd rather suffer through a hand and foot attack then to have a laryngeal attack. My children watched me leave my house when they were 3 and 5 years old on Christmas Day. I'll never get that back but I was having severe attacks. Every time I leave my house to go to the ER my children are terrified mommy is not coming home. Like Tony, I'm a lucky one. My story is very boring but I have many members of my family that have this disease and not having access to medication is detrimental to our health.

MS. BEITER: I think something that is really important about what is up here is that we wait until there is pain or discomfort that is intolerable is that I know for me, my story doesn't go nearly as long as a lot of people in the room. I had so many years where doctors chalked it up to really weird things or just wrote

me off. So, a lot of times I convince myself that maybe it's not an attack until it becomes intolerable because then you're like, well I guess this is what it actually is. So, I think that 43 percent sort of holds that true to a lot of feel that like we can say, oh maybe I have a cold or maybe it's just a headache or maybe I just don't feel great this morning. And then four hours later, we're in that intolerable discomfort. I think a lot of us do that as well. I've heard people say that they wait too long because they think maybe it is not necessarily all know exactly what it really is.

MS. LIPSCOMB: Thank you. Was there anybody on the web?

MR. PIERCE: Just one web participant, David, mentioned that he treats when symptoms are recognized, he does not wait until they interfere with his activity or become intolerable.

MS. BOUCHKOUJ: Also, Jennifer from the web is echoing what Ross just said. If they don't treat the first attack it's really hard for them

to get a hand on taking care of the rest of the attack.

MS. LIPSCOMB: Thank you guys. So, let's talk about your decisions of choosing different treatments or how you choose one treatment over the other. Aside from the cure when considering a new treatment for your condition, which benefits would you consider the most meaningful, and you can choose up to two. So, reduction in attack, frequency, reduction in severity, rapid response to treatment of acute attacks and completeness of response to treatment out of acute attacks. So, we hear we should have said all that apply. My new obsession is Hamilton so I feel like we could say you should have been in the room when it happened. Can we see? So, for us is reduction in attack frequency and you kind of did answer more than once considering B and C are almost a statistical tie. What does the web look like?

MR. PIERCE: So, reduction in attack frequency and rapidity of response are getting the

highest responses but just by a small margin. Next is reduction in attack severity and lastly completeness of the response to treatment of acute attacks.

MS. LIPSCOMB: Okay. Do we want to talk about the two choices that they picked? I didn't talk to her last time so I'm going to pick her.

MS. NEAHRING: For me, being in college it's important for me to be able to get back into the swing of things quickly. When I miss, I have one class that's three hours so if I miss that class once, I miss a whole week of material. But I also think it's important to mention that some people don't have a choice in their medications. So, the beginning for me because I was a patient with normal C1, I was given two options for acute attacks. I didn't get to pick which medications I was on, I didn't get to try different ones so some patients don't have that option.

MS. LIPSCOMB: Thank you.

MS. SANTEE: Well, to piggyback, on what Kelsie said, we have the same type and rarely can

you participate in the acute side of things. However, I was diagnosed a little earlier so I was able to try the prophylactic even though we thought it may fail, it did. I was hoping and praying that it would work for me and that was Cinryze. So then after that, I had to get back on those dreaded androgens and yes, it did blow me up so I do understand. But then the acute attacks came, the acute rescue medicine came. The first was Kalbitor. Unfortunately for me, as I told you earlier, I had a young son I had to take care of and he also had health issues. So, having to have that administrated in the hospital was not a good fit for me. So, I went to Firazyr when that finally came aboard and that has given me a little bit more autonomy. However, I'm here today because there are new medications that perhaps are on the same vein of our acute medications that we have, may provide prophylactics. I think that I answered A and B and I'm just hoping that A and B can really be preventing attacks and not even B being an issue because I won't have an attack to

have severity. But research is so crucial for some of us who don't have options to flip flop to and I just thank you for having us here. We definitely have to continue, like they said, there is not an option for everyone. We all have variability in how we respond to certain attacks. I just really hope that we can get a prophylactic for people who only have the rescue medication.

MS. LIPSCOMB: Would you like to talk about the treatments?

MR. COSTALDO: So, the good news is about the HAE with normal C1 inhibitors, there is significant amount of research being done. As a matter of fact, down at the angioedema center at the University of California San Diego, they probably have seen more normal C1 inhibitor patients than just about any center in the United States. They are taking the blood samples and they're really thinking it through. We have some really incredible scientific minds that are looking at it and I wouldn't be surprised, if at some point, they're able to come up with a

biomarker which simply means that they can then better look at what the cause is and then determine what an appropriate therapeutic regimen might be.

So, normal C1 inhibitor right now, HAE with normal C1 inhibitor is still a brave world, if you will. There are lots of elements of it that we just don't understand but we're very excited about the work that's going on at the angioedema center and their focus and the Hereditary Angioedema Association has really been very active in making sure that that research is being funded. The Angioedema Center also apropos some of the things we've talked about here with the treatments, they're looking towards this notion of precision medicine. This has nothing to do with the regulatory side of things because our wonderful friends at the FDA, they are responsible for reviewing candidate medicines and approving them for license. But there are other types of research being done that can actually look at a current medicine and find maybe what is the right

dose, the right incidence of taking the disease and so forth.

One other point I want to make and I think is important for all of us here sitting in this room and that is as we get better preventive therapies and if you look at what is being thought about in the pipeline. Currently there is Lanadelumib is in the clinic. Haegarda was just approved. There are probably going to be clinical trials with the kallikrein inhibitor pill form probably next year, if I read the press releases correctly. There are two other companies that have pill forms, kallikrein inhibitors that are looking at it. There is also a trial going on with a pill form for acute. I can tell you also that two other companies have been in touch with the HAE Association that are looking at gene therapy solutions for this disease. So, there is a lot going on out there right now. So, just keep in mind that all that is happening because we also want to make sure that everybody is willing and continues to be willing to go and participate in

clinical trials as we go forward. So, stay tuned folks, there is a lot in the hopper.

MS. LIPSCOMB: Well, since he's led us to the clinical trials question, we're going to go to our next question which is the precursor to the clinical trials question. So, which of the following factors, of the following factors, which three would you rank as most important to your decisions about using treatments to treat your condition. Again, use up to three. How the medication is administered, how frequently the medication is administered, access to treatment, possibility of common and non severe side effects, possibility of infrequent but serious severe side effects, previous improvement in response to a similar treatment, previous lack of improvement from another treatment.

MS. BEITER: can you explain the G?.

MS. LIPSCOMB: I can and I can explain it by walking over to Larissa and letting her.

DR. LAPTEVA: So, I guess it's the G that needed to be explained. If you've previously

used some type of treatment and it didn't work for you, would you choose that treatment or category of treatment again or would you choose something else? You would obviously choose something else. So, that's something that would influence your decision to choose your next treatment and that's the G. Did that help?

MS. LIPSCOMB: Thank you. Let's go ahead and close this poll. So, in looking at the top three factors, the first one, how the medication is administered, is the most often cited followed by access to treatment, cost insurance coverage. And then almost a tie between B and E really. How frequently it is administered or the possibility of infrequent but serious and severe side effects. How does the web pair up to that?

MR. PIERCE: It really looks very similar.

MS. LIPSCOMB: Okay thank you. So, it looks like to me that really, and I think we've heard about PICC lines and ports and sterile

environments that there is a lot to go in when you think about what medications you want to use. Is there anything else about a treatment that you're thinking about before we go and ask the questions?

MS. TUMA: My name is Stephanie and I'm concerned also about like long term effects of these medications. Like I'm 25 years old now, if I'm still taking this medicine at 75 years old, through the next 50 years if I'm on the same treatment, what are the side effects going to be for that?

MS. LIPSCOMB: Okay. Anybody else want to comment?

MS. BRAHEN-GRISSENBACK: Peggy. I didn't get a chance to vote for all of these but it depends on each of these becomes important in different situations. Like in travel or my husband helps me infuse. If he has a migraine or something or he's away, how the medication, if I can use subcutaneous. And then the other one is like again, I'm older now, I'm 62 years old so that's something I was thinking about for long

term effects. It's like okay it's going to help me now but it's going to take 30 years for it to damage my liver. Well, okay if it's 30 years to damage my liver, I probably don't have 30 years to live so maybe I'll do that one as opposed to somebody that is 20. They really have to think about that. So, I think, again the different situations you have and the different age and how some people's attacks come within 10 minutes, some people's come within a day. So, again it switches back and forth. And then insurance, I have good insurance. Other people, they can't the treatment, they don't have a choice because of insurance companies.

MS. LIPSCOMB: We'll take one more and then I'm going to ask the FDA panel if you have any follow up questions.

MS. FRENCH: There are so many decisions we have to make on a personal basis about all of those. One of the decisions we don't get to make in some cases is C. Because what the FDA does and all the hard work they put in about how the

medication should be given and the quantity per day because of the data that we have given them, what is your insurance company balks and say you're supposed to be able to take three doses per day but your medical insurance says well I'm only going to give you three boxes a month. What do we do then for the other 20 something days and have an attack when you in your wisdom and us in our hard work have proven otherwise? So, sometimes C is taken out of our hands and is not even a choice.

MS. LIPSCOMB: Thank you. The panel, do you have any questions?

MS. PUROHIT-SHETH: Hi, I'm Tejashri Purohit-Sheth and I want to go back to the question that was asked of you regarding the prophylactic treatment. So, many of you picked other. I was very interested in learning what other therapies for prophylaxis have you been using outside of Danazol, Cinryze or Haegarda. Thank you.

MS. RAMSEY: I have been using the

Cinryze and with the recent manufacturing problem, I was out. I was lucky enough to have access to Ruconest. Unfortunately, I'm having small episodes start after I do a dose. So, three or four days past and I start to have another episode. So, I'm practically on the same prophylactic schedule, I'm just experiencing that kind of lack of C1 is triggering episodes for me. So, it's practically prophylactic for me right now. I know it's off label so that's why I was reluctant to raise my hand earlier but that's the situation I'm in. I responded very well to the Cinryze and it was a literal life changer. The Ruconest has been great but if I try to go without, I end up having another episode start. I know we talked about the importance of treating when we see the first signs.

MR. MALLORY: I'm Mike from Ohio. I've been treating prophylactically with a study medication that has been working very well for me.

MS. LIPSCOMB: Thank you. Anybody else? I'll get you, Dakota.

MS. THOMPSON: Thankfully, I have been able to actually get on the clinical trial for Lanadelumib so I'm no longer actually taking a prophylactic but instead, just taking part of a research trial.

MS. LIPSCOMB: Okay thank you. Anybody else on the panel?

MS. PUROHIT-SHETH: I have one more question. Many of you mentioned that you have some warning symptoms before your swelling actually starts. I was interested in understanding what some of these warning symptoms felt like.

MS. FOX: I'm Debbie. I get the rash the rash and also just extreme fatigue like you can't go another step.

MR. SELSOR: I get that rash too and before an abdominal attack I'll get a specific vague headache. It's the only time I'll get it is the day before.

MS. STARR: I get very dizzy, lightheaded and that's one of my first signals.

MS. NEAHRING: Fatigue is a big one for me but also severe dehydration to the point where I'm drinking water and it is not helping resolve the dehydration and the cotton mouth.

MS. RAMSEY: I'm Adina. For me, I'm fortunate that most of my episodes are on my extremities which is kind of a downfall because it is easy to overlook those. I'll feel a tightness or an ache. My knees are really bad about it and I'll try to wait to see if it is and then it starts to show that red area so I know and I infuse.

MS. EDWARDS: I'll get abdominal swells and I can't recognize it unless I have cramping before until my stomach has already cut everything off and it is just these putrid burps. And at that point in time, even taking Berinert right then, I still have like a two day attack. Everything has got to go through and up and out but it's not as severe as it used to be which would be days and days.

MS. SANTEE: I have a lot of peripheral

limb swelling as well. Even on my face I get tingling or a little itching. It's not itching like a normal itch but a sensation. Hours later, that area typically will swell.

MS. BOMAR: My name is Fran. I have many of the pre symptoms that a lot of these folks have talked about, fatigue and so on. One of the things that I think is interesting is I feel like I'm an out of focus picture. I can't keep moving and I just don't feel right. The other thing, also my white eye gets so blood shot and painful I can't even look at me, it just makes me cringe. As soon as the attack comes on, the redness goes away.

MS. RENDON: My name is Amy. I don't have HAE, Dakota does. Prior to her being on a prophylactic, I used to be able to tell her within 12 to 24 hours when she would have an attack because she would get what I dubbed, HAE PMS. She would get cranky and short tempered and just not happy. So, there was an emotional side to it that she also gets the rash. At one point, a surgeon

had called her telling her he wasn't going to put in her port. He was on the phone with her and I literally watched the rash crawl across the her neck. It scared me to death. I took the phone from her and would not let the surgeon talk to her any longer. What he was saying, literally, I watched him send her into an attack. But there is a HAE PMS, I'm telling you.

MS. LIPSCOMB: I think we have some --

MS. KASS: Donna, I have one more.

MS. LIPSCOMB: Okay let me talk to the people on the web first and then we'll get there.

MR. PIERCE: Diane on the web says, that she feels like she's done too many sit ups and then the swelling because obvious afterwards. Her waist circumference goes from 37 inches to over 40 inches during the attacks. So, some people think she looks like she's pregnant when she's experiencing an attack.

MS. BOUCHKOUJ: Also, we have some other comments that some of these symptoms include bad breath and foul smelling gas. So, that can happen

just before the attacks.

MS. LIPSCOMB: We have one more.

MS. BARNES: I'm just going to reiterate what Amy said, she kind of talk my line. Jim, when he was 5, I could always see an episode coming because he was moody. We didn't necessarily call it PMS. It's putting up with Momma. He had a lot of the behavior and the irritability, I could see within a day or two and then he'd sleep a lot. And then after the episode, it was the opposite swing of the emotional pendulum. He would be real sappy and sweet and overly affectionate. So, that was like a rebound for him but I could always tell when he was getting ready to have one with the rash and everything too.

MS. LIPSCOMB: Okay, thank you. Any other questions? Okay thank you. So, I think that's an easy lead into our next discussion topic. We're going to go to topic three which is the possibility of clinical trial participation. Now, I'm pretty sure I heard a couple of you say

you've been on clinical trials, you believe in them. I heard a cheerleader back there so I think this will be an interesting conversation for us. So, these are really kind of what I want you to think about when you're answering the questions. So, if you have the opportunity to consider participating in a clinical trial studying experimental treatments, what aspects would you consider when decided whether or not to participate. If you have previously participated in clinical trials, discuss your own experience whether favorable or unfavorable and explain why you chose to participate. So, if you had the opportunity to participate in a clinical trial with investigational treatment, which of the following best describes your thoughts. Yes, I would consider participating, no I would decline the offer to participate and maybe depending on various factors. And you know we're going to talk about those various factors. So, only 5 percent said no but 65 is a resounding yes and 30 percent maybe depending on various factors. How did the

web look on that?

MS. BOUCHKOUJ: No one said no, so they would all participate in a trial. Some of them it depends on various factors.

MS. LIPSCOMB: Okay great. And although several products have been made available -- I see a hand up, tell us about your decision.

MS. THOMPSON: My name is Dakota again. Like my mother mentioned in the first half, I became septic and nearly died last year. I went to, ended up getting my port removed, got my PICC put in and I went to go talk to my specialist about new medications like what to do from there. He did not trust the research trial if there was going to be a placebo in it. I swelled way too much, way too often and way too severe to even consider taking a placebo. But I was able to join the current trial because it's open label and I know I'm getting the medication daily. So, the factor is that I need to make sure I don't end up in the hospital constantly because of my attacks.

MS. LIPSCOMB: Thanks. Anyone else want

to talk about their experience?

MR. MALLORY: Hi, I'm Mike from Ohio. I chose to be involved in as many clinical trials as I could when my wife and I were having our first child because I didn't want my child to suffer the way that I have. We've seen a lot of great medications come along and out of my three children, my youngest daughter is the only one that is currently diagnosed with this disease. I want to have better treatments for her if she ever does start presenting with this. So, I participate as much as I can in hopes that she never has to suffer.

MS. LIPSCOMB: Thank you.

MS. BRAHEN-GRISSENBACK: I participated in one of the clinical trials but it was either you got the drug or you didn't get the drug and there was no escape clause in terms of, I unfortunately got the saline because I had to drop out because I would ended up in the hospital because almost every day I was attacking. So, I guess when the clinical trials are brought up,

there has to be some way to, since it is all so stressful and mental, to allow the people to know that you can escape or get the real drug or open label if it's not working for you and you're seriously suffering.

MS. LIPSCOMB: Thank you.

SPEAKER: So, Dakota brought up a really good point, both speakers brought up a good point. And that is, at what point does an institution review board determine that maybe a placebo is not appropriate. I don't know the answer to that. I think that's something though that as current treatments get approved and are more effective or are affective, particularly the prophylactic treatments, at what point do IRB's or even patients begin to wonder, can I afford to participate, do I want to get sick if I've not been sick before. That is an ethical and regulatory decision going forward that I think is going to be interesting.

MS. LIPSCOMB: Thanks. I think the next question --

MR. GOLDSMITH: I just wanted to talk back to the issue about open label. No trial should have less than the standard of care. You either get the approved therapy, you have lots of them, that's the standard of care that has to be the comparator for a licensure trial. You can't get less than that, that wouldn't be an ethical trial. So, if it's an open label trial often it's because they've already finished the testing phase of the drug and they've enlarged the access because they have promising data. They have a treatment entity and they let other people come in the trial and get the drug. They get additional safety and efficacy information from that group. If they are approved therapies, that's the standard of care. You can't get less than the standard of care.

MS. KLINGER: So, are you saying in a phase one trial for an angioedema drug, the placebo would be an approved therapy not a placebo?

MR. GOLDSMITH: It's a phase one trial

so a phase one trial is really a safety trial. It's a first look in humans of the use of that drug. So, it's important to have a true placebo to understand what the adverse effects are that you can attribute to the drug versus what you might attribute to getting the placebo.

MS. KLINGER: I guess that's what I'm asking because you just said it wouldn't be ethical to have the standard of care --

MR. GOLDSMITH: In a treatment trial right but that's a safety trial.

MS. KLINGER: Right, I actually work in clinical trials in an academic medical center in clinical trials administration. So, I do think that that's a problem not just for hereditary angioedema but for other serious rare diseases. As you've heard today, going with a placebo is life threatening for us. So, I've participated in a clinical trial for the same reason as Mike. I have two kids, I don't want them to go through what I and my family have been through. I understand the importance of the first in human's

information and data but maybe there's a discussion that needs to happen about what is the difference. If you can blind the treatment and know that one treatment is an approved therapy and one is the first in humans, then why is that data any worse than the other. I know with the placebo you risk. If you want to talk about SAE's, death is certainly the worst of all of them and we wouldn't want to put people through that possibility.

MR. GOLDSMITH: Right I'm not arguing about that but most of these are like single dose. It is a placebo controlled trial but it is a single dose or it is multiple doses and it won't go on terribly long, those studies. They might be two week studies, four week studies just to get an idea. Because if there is some terrible adverse event with a new trial it will probably show up right away. You don't know, you don't have equipoise because you do trial work. You don't know if the new therapy really is better. It may have been given in an animal model if you're lucky

and you know something about it but it may not. There's kind of internet chatter of this is a great drug. The quickest way to licensure is to a double blind prospective controlled trial. That gets you the most data in the shortest time. If you randomize from the first participant in a trial, you'll get that data even sooner. It is a hard undertaking.

I know there was recently an approved therapy for spinal muscular atrophy. I know the community thought long and hard about doing a gold standard trial but that's what they decided to do. The families volunteered to be in a placebo arm. That trial was cut short. It was scheduled for 140 people. It was analyzed with 85 people. We did our review in about three months. It just truncated the process dramatically because it had a good effect. So, if you can get to that, I think that's what you should aim for.

MS. LIPSCOMB: Okay we are getting close on time so let's go ahead and get these next questions. They are really centering on this

conversation that we had already. The next one is, what reasons would influence your decision for the study. This is exactly what you were talking about. Keeping in mind that to participate in some trials you might need to temporarily discontinue your current treatment or receive a placebo for a period. So, this is given everybody a chance to have that conversation. These are the reasons you would do this. My current treatment causes side effects, you think your condition is well controlled and discontinuation of my current treatment will not result in occurrence of new attacks so I'm willing to participate or I think my condition is well controlled but I'm willing to participate as long as I can receive proper treatment from an FDA approved product, should attacks occur. We'll give you a minute to answer this and then we have three questions we'll do at once and summarize. So, it seems like as long as you can get some treatment you'd be willing to do this. The next question is, so newer treatments are being developed all the time and many gene

therapies hold promise. It's extremely important to know how you're thinking about the benefits and the risk. So, even if there's the treatment might result in a cure but carry a small risk for a serious side effect such as cancer, would you be willing to participate.

MS. PERRY: We can fix HAE.

MS. LIPSCOMB: Point taken. So, what about the web?

MR. PIERCE: So, the most popular choice was maybe followed by no. 10 percent of respondents said yes.

MS. LIPSCOMB: Okay. Let's go to the next question. Would you be willing -- so for rare disorders including genetic, it's important to collect data to better understand the natural history. So, in these kinds of clinical trials, you won't be getting any particular treatment, they're just going to kind of follow the monitor you over time. Would you participate in this kind of study.

MS. FOX: You can continue?

MS. LIPSCOMB: Yes. They're really checking you on your treatment so yes or no. Let's go ahead and close that. So, most of you would do natural history.

MS. LONG: Can I just say, Donna, the US HAEA has a scientific registry which does this exact thing. So, it may account a little bit for the 100 percent but this is something that we value as well as very important to trace the history of these new medications as well within our patients and the effect on the quality of life.

MS. LIPSCOMB: Okay thank you. I think we've talked a lot about clinical trials. Does anybody want to make sure that their voice is heard in how you think about clinical trials, whether you participate?

MR. WILLIAMSON: I feel that as a community we've had access to medication for such a short time, most of us do remember what the dark ages were like. Therefore, a lot of us don't want to be complacent in our treatment and a lot of us

still want to strive for better treatment, not only for ourselves but for our children because we haven't had access to treatment that long.

MS. KLINGER: I just want to speak, this is Lydia, from my professional side of the coin. I've been working with clinical trials administration for about almost two years now. I've been in an academic medical center for 11 years. I think a part from the patient side of the coin, the regulatory and administrative burden of getting clinical trials started, which I'm sure you guys hear about all the time, actually deters physicians from even becoming researchers. So, I think that we certainly need to do a good job as patients of advocating for ourselves and letting our providers know what risks we are willing to accept. I remember seeing the inclusion exclusion criteria for a study for Sjogren Syndrome recently where part of the criteria was that you couldn't have ever taken a biologic treatment which pretty much excludes everyone with that disease in a lot of cases. So, I think that from the FDA

perspective, just considering, and you guys probably already do, but some leniency for diseases like ours where while we don't want to get cancer, I'm okay with hearing that I may feel nauseated because it is probably not going to be as bad as the nausea I experience when I'm having an abdominal attack. I'm okay with understanding that every clinical trial has some risk of a serious adverse event if I have a physician or researcher who can really explain what that means. All those drug commercials now with the long, long list of things that happen to a fraction of a percentage of people in the study. I think those are important things to add when you're asking questions like, would you be willing to take on the risk of getting cancer. Well, what is small. If it's a 5 percent risk, well no. But is it's a half of a percent, maybe I would. Just kind of considering those things when you guys are reviewing new trials as well.

MS. BOMAR: Back in 2005, I had reached such a low end that I was willing to do anything.

That's when the (inaudible) trial which was the first in a long while which has turned out to be Cinryze, opened up. They told me the good news after I went there for two weeks to qualify that I was sick enough to be in their study. I had never been so happy in my whole life. So, that lasted almost three and a half years and it was a double blind. I kissed the ground that they walked on because Cinryze changed my life absolutely. Over the years, and I have been on it since, over the years I have been asked by various people would I be willing to become part of another trial. I would have had to have given up Cinryze. I was not willing to do that. I finally had a quality of life and I wasn't

going to give up a known for an unknown. If it ain't broke, don't fix it. Cinryze, who knows what the production of it is and I'm waiting for Haegarda. There may be something that will be a possibility and I will still have to think about that very carefully.

The other thing that I learned in changing from Cinryze to Haegarda is an insurance situation which really stunned me. Because as expensive as all these medications are, I'm on Medicare with a Part D. So, I was walking out with thousands of dollars' worth of medicine every month with no copay. Well, when I got a phone call that said, oh by the way dear old person, you're at the donut hole and now for the first month you'll have to pay $2000 and then the second month you have to pay $5000, I went whoa. Who can cough that up. Well, obviously there is assistance out there and I have pursued that and so we're on the road to do that. Which then

brings me around to, we are in Washington, D.C. Congress is once again going to be messing with our preexisting conditions along with other things. I wonder, I do question, has anyone in Congress ever had a chronic illness? Has anybody there been sick? Does anybody know anybody who has been sick because once you have, you wouldn't feel the way a lot of people do. My cry is for people to do something about that and to press people that we exist and we have preexisting and some people are born with preexisting, there is nothing we can do about that. You can't be taking our insurance away from us or our help away from us.

The other thing is, I did want to ask, this is the first time Cinryze has been in a shortage or manufacturing issue. Does anyone have any kind of control or pressure over these kinds of pharma companies to make sure that there is regular supply or are we just at the mercy of this situation because it is really a frightening prospect for all of us sitting in this room.

MS. LIPSCOMB: Last comment and then we'll see if we can address an issue.

MR. EDWARDS: I'm Miles. One of the things I wanted to say about being able to get a hold of the drugs and get it properly, we've had drugs shipped to us that were supposed to be refrigerated that were not refrigerated. We've had wrong doses, we've had the doses mistranslated. A lot of the pharmaceutical companies do not know how to supply correctly. Personally, for my wife, I had to go up against the general counsel of a major drug provider and the general counsel of a major insurance company just to be able to get the proper medication for my wife. That is our only recourse that I've seen at this point that we have and if you don't have what it takes to stand up against general councels than you're doomed. I don't know how many people have that strength.

MS. LIPSCOMB: Thank you very much. I think this is one more chance to ask the panel if you have any questions. Right now, we're a little

behind. We're going to do the public comment period and we have four speakers. They'll be doing about five minutes each and then we'll kind of close up.

MS. WARREN-HENDERSON: Good afternoon, everyone. For the transcriptionist, I'm Lonnie Warren-Henderson. First speaker, Paula Busse, Mt. Zion Hospital.

Dr. BUSSE: Hi, my name is Paula. As I mentioned before, I take care of a large group of patients with hereditary angioedema which I feel very fortunate too. One thing that we've been talking about is the designs of the clinical trials. It does bring a really good point up about the use of placebo and some of the designs. I don't feel right asking my patients to participate in trials if they -- I don't want them to feel obligated to me to come off of a medication. I understand some patients will do that because they want to get better therapies but it puts me in a bind and that's not good for the community of patients with HAE. If there is some

way that we can design better trials or formats using somewhat of historical data on patients or have a guarantee that we have crossover studies where all patients get medications. I know you have to show that the drugs work and I understand that, the reason for placebo but it really makes it difficult. Part of the goal for HAE therapy is to have patients have medications that can be given easily and conveniently without the use of injections and really to have patients maintain a good quality of life. I would just like to put a plug in for easier designs for patients to participate in trials.

MS. WARREN-HENDERSON: Thank you. Second speaker, Mark Riedl, University of California San Diego.

DR. RIEDL: Good afternoon. Thanks for the opportunity to say a few words. I'm Mark Riedl, I'm a physician at the University of California in San Diego where I work at the angioedema center there with my colleagues Dr. Christiansen and Dr. Zuraw. A couple of quick

thank yous. First, I want to thank all of the participants here, the patients and their families. I hear these stories, I've heard hundreds of these stories and the good news is you never get accustomed to hearing these things. We should never become accustomed to hearing what you all go through. It is just a very poignant reminder of why we in healthcare do what we do regardless of the condition. We need to continue to work as hard as we can to prevent suffering and prevent these conditions from derailing people's lives. So, thank you for sharing your stories. Also, thanks to the FDA for this opportunity. It is actually very encouraging to know that you all are engaged and listening to patients. You have a tough job and I think it's very important that you're here from the people that are affected as to how this affects their lives.

I'll be brief but three quick points and you've heard all of these already today but I just wanted to punctuate what I see from my chair in taking care of a very large group of people with

HAE. The first is that while we've made a lot of progress in the last several years, we now have medications that have been shown to be effective and safe. We have not reached the finish line and I actually think we have a lot of work to do to make this, what I like it to be, which is a very quiet, predictable chronic condition. I think a lot of the stories I heard today show that. This is far from predictable so far. It is still very unpredictable and very troubling and disabling to a lot of people. So, pursuing medicines that will lend that predictability to this condition, that's sort of the holy grail in my regard. We haven't reached that point so we have work yet to do with developing medications.

The second point that you heard about is variability. It's absolutely true as you heard from some people that we do see individual variability to these medications. So, while big studies are great to show that these drugs work generally for a group of people, there is a lot of variance and one of our struggles has been trial

and error of figuring out which medicine works best for each person. I think Tony or somebody mentioned precision medicine and we've had an interest in precision medicine. It takes funding to do those sorts of studies but we're hopeful that pharmacogenomic studies will be better at determining what works best for each person. Because of that, we need a toolbox of choices and while we have some now we could use more, in turn, because we still have patients that are non-responders or have bad side effects from some of the medications.

The third point is the pediatric issue. We really need more access to medications for children. We all recognize the challenges of doing pediatric studies and it is a vulnerable population that we don't want to cause any harm. But we really have very limited options for children right now. As you heard some of the stories, one of them was severely affected groups of people and they have severe symptoms. Just a plea to the FDA, I know you're working on it, I

know the companies are working on it but whatever we can do to accelerate treatments for children would be of great benefit. Thanks very much.

MS. WARREN-HENDERSON: Thank you. The third speaker is Sandra Christiansen, also UCSD.

DR. CHRITIANSEN: I may be a little less eloquent than my predecessor and colleague, Dr. Riedl. I would like to first mention that there is really nothing to add to the heartfelt stories that people have shared with us. As was mentioned, they still tug at your heart and we have work to do. The career that I've had has spanned over 30 years in HAE so I remember when we had nothing. We didn't even know why people swelled and it has been very gratifying to watch the arc and see what we have now and we're very grateful as our the patients. I think we owe a testament to the patients that have participated, the pharmaceutical industries that have helped develop these drugs and the science and the FDA and I thank all of you.

Mark made a point that I was wanting to

emphasize which we do have a current unmet need in addition to our wish for a brighter future, which is children. We have a single approved therapy for all ages and it is intravenous plasma drive C1 inhibitor. It's not a special qualification but I'm also a mother. I can't imagine if one of my daughters was suffering and in pain and the only thing I had to do was start an IV. There is data which, I believe, has even been presented to the FDA, on trials in children down to the age of two, showing safety of a sub Q treatment for acute relief, icatibant. We've heard the troubles with clinical trials and ethical issues and I would not wish perfect to be the enemy of the good. I would hope that the FDA would consider, for this country, that it would be appropriate to approve for children what is going to be approved for children in Europe. We also have no prophylactic therapy that has been approved for children. We have safety data, we know things that work and as Dr. Busse was saying, it is a huge, huge burden to get drugs approved for

individuals. If there is no indication, it is almost a full time job battling with third party payors. So, again low hanging fruit, data we have, safety we have, need we have, I would hope that people would really urgently consider this while we again, hope for more developments and more improvements. Thank you.

MS. WARREN-HENDERSON: Thank you. From fourth and last speaker, Bruce Zuraw, also UCSD.

DR. ZURAW: Thank you for the opportunity to speak and thank you to all the patients who told their stories today. I've been working in HAE since 1983 taking care of a lot of patients over that time. I feel like as I listen to your stories, I was reliving history. The pain that we all went through early on, the lack of treatment and the remarkable progress that has been made. Obviously, the FDA has been very important. Pharma has been tremendously important and we've come a long way. But as the stories also pointed out today, we're not there. And as my colleagues mentioned, there is still a lot of

problems, we're not at all happy. I recognize the progress but we're not going to stop where we're at.

Another issue that has come up repeatedly that we heard today was the trouble finding a physician who would listen, who knew how to treat the disease, knew how to diagnose the disease and how do we deal with that. I would like to make a plea and I know that he FDA has been good about this. As a physician investigator, I threw in my hat many years ago with the HAEA deciding that if there was one group that could get the word out that could tell patients where they needed to go, what they should be doing to get the right care, it was the patient advocacy group. I encourage you to continue to work closely with the HAEA. I think they are the honest broker in the room. That's the way that patients get to them through the website and get diagnosed and then get treated.

So, I'll make a couple of last quick points. The FDA appropriately is concerned with

unmet medical needs in deciding as you go through new drug applications how you gauge an unmet need. I think it's important to recognize that it's not just abdominal and laryngeal attacks that represent an unmet need. As we've heard today, hand, foot swelling, really puts people out of work, out of school, goes on often to involve the abdomen and throat if they weren't treated with on demand drugs. I think any attack has to be treated as a serious problem and should be recognized as such. And that as you think about the need for new and effective drugs, we really need to get people to the point where we're not having attacks at all before we can say that we've reached where we want to go.

My final point and philosophically, I think it's an important one and it doesn't come up very much in medicine. If we can simply replace C1 inhibitor or inhibit kallikrein or perhaps factor 12 adequately, we have a disease now that is life threatening that is very highly morbid that we could essentially completely control.

People would be totally normal if we could simply interrupt that one pathway. It's a real opportunity to do something that we almost never get to do in medicine which is to make people completely whole. I know it keeps me going in this field wanting to push forward and I hope the FDA realizes the opportunity that we have as we move towards the future. Again, I want to thank you for having this meeting and for listening to all of these stories all day. Thank you.

MS. LIPSCOMB: Thank you. Well, I can't thank you enough. We're going to invite Dr. Larissa Lapteva up here to summarize the meeting and she's actually going to say goodbye. But I'm not leaving here until I tell you how moved I was, how appreciative I was that you were able to tell me your stories and your experiences. I will be forever touched by what I've heard. Thank you so much I can't tell you how appreciative I am.

DR. LAPTEVA: Good afternoon. So, we have come to the concluding part of our meeting. It has been a day full of honest sharing,

compassionate understanding, vivid descriptions, moving stories and above all, hope for future treatments, for new therapies that can change the course of HAE more so than the currently available treatments.

On behalf of my colleagues, I would like to extend our appreciation to the participating patients and families, to all those who came here in person and those who participated with us online. We have learned and will continue learning a great deal from you. Today we heard about what patients and families care about, what worries people and what makes them feel better and what kind effects they would like to see from their treatments. In the next few minutes, I will try to summarize some of the issues that have been discussed.

During the first session, we heard about frequent delays in the diagnosis of HAE. Over 50 percent of people who participated in our poll here in the room said that the time that took from the initial symptoms to the diagnosis was about

10 years or longer. By having meetings like the one we had today and by continuing the efforts of multiple stakeholders including healthcare providers and patient advocacy organizations, we hope to improve the recognition of this rare disease.

We also heard from patients who have a family history of HAE, from patients who are adults and also from parents and siblings of children and adult patients who live with the condition. We heard about the unpredictability of the attacks and how it actually is to live with this feeling of unpredictability, not knowing when an attack will come and what part of the body it will involve. We heard about the painful abdominal episodes that often require medical care, even intensive care to be treated to resolution. Many people mentioned the discomforting, painful and disfiguring attacks of different body parts that interfere with all activities of daily life, prevent going to work,

to school, prevent from doing any kinds of social activities. Many people are unable to care for themselves, for their children, feeling left out. We have also heard about the exacerbating effects of HAE on some activities that many of us who don't have the condition, may take for granted which may range from exercising or doing some repetitive motions to getting dental work done, or gynecological exams, to giving birth to a child and sometimes simply being excited, or happy, or stressed about something.

A number of people commented about the influences of hormonal background, particularly in female patients that often are experienced during the adolescent years as well as peri menopausal years. Depression, anxiety, fatigue, drug seeking accusations, and unnecessary surgeries remain a reality for the HAE community. Many people mentioned their greatest fear and their biggest concern which is the possibility of developing a laryngeal attack and not being able to treat it rapidly and affectively. Endotracheal intubations

and tracheostomies do remain not to be an uncommon practice. We heard about the life changing experiences with the availability of treatments for HAE. And even more so, the vital importance of not only attack treatments but also prophylactic treatments.

Over 60 percent of folks who participated here in our poll in the room, do receive prophylactic treatments of different kinds. The importance and the place of prophylactic treatments cannot be overemphasized. They significantly improve the quality of life, they increase the time between attacks and, more importantly, provide peace of mind to patients and families.

In terms of product benefits, most of our poll participants indicated that in the new therapies, they look for both a reduction in attack frequency and attack severity. Although, I do recognize that that question really called for all answers to be yes. You would want to see a reduction in attack frequency and severity and the

rapidity in the response and the completeness of the response. Yet please also recognize that this information does help us to better guide product development. In addition to various sources of scientific information that we take into consideration, this helps us to better design future studies and select study endpoints. So, thank you for answering all of these different questions.

In terms of risk, people remain concerned about various side effects. Common side effects may not be as much of a concern. Only 7 percent of people said that they would take them into consideration. Serious but uncommon side effects remain the concern. But again, the adverse effects as was mentioned by a number of participants, would need to be taken into consideration within the framework of the benefits that you would get from the treatments. So, we always take it as a benefit risk assessment.

From what we've heard, there is still a long way to the cure and to the complete control

and prevention of each and every attack that may occur in each individual. There is still a need for less invasive therapies, for therapies that take into consideration the hormonal background and hormonal changes that may occur in patients. There are still issues with IV access, there are still issues with infections, so we do need better treatments, newer treatments, more helpful treatments.

There is still a need to observe long term effects of the current treatments and to develop newer treatments, not only for adults but also for children and to ensure smarter designs of future drug trials. These include methodologies that could help collect patient input and incorporate input of patients into the products' benefit risk assessment. Our polling questions results here in the room showed that about 65 percent of patients would like to participate in clinical trials. 100 percent of people would want to participate in observational studies.

So, following this meeting, we will summarize the discussion and the lessons learned in the Voice of the Patient report which you've heard about, which we'll post online. While here at the FDA, we continue our efforts to facilitate the development of safe and effective new treatments, it is really the voice of patients that guides us in the right direction. Patient advocacy is very strong among the HAE community and today's meeting really would not have been the same without the tremendous support of the HAEA. On behalf of my colleagues, I would like to thank the association for always taking the proactive stance in supporting their community in many aspects: from distributing relevant information about the disease to patients and families, to promoting the development of new products, to providing substantive support to the community in times of product shortages and much more. Thank you for doing the great job that you do. The work of patient advocacy groups like yours remains of utmost importance to all of us.

I would like to thank everyone who helped to organize this meeting. It was really an effort coordinated across the FDA with participation from different centers and offices with the leading role of the Center for Biologics Evaluation and Research. And much appreciation should go to the office and the center leadership for their endorsing and very attentive support of not only this meeting but also many other collaborations related to patient advocacy and to incorporating patient input in developing new therapies.

Finally, I would like to thank all the participants of today's meeting. As healthcare professionals, researchers, industry partners, FDA staffers, regulators, we humbly learn from you, the patients, every day. And today's meeting is yet another testimony of how much you can tell us in order to help moving medical progress into the future. Thank you for that. Thank you and safe travels back home. We're adjourned.

(Whereupon, at 2:50 p.m., the

PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

I, Carleton J. Anderson, III do hereby certify that the forgoing electronic file when originally transmitted was reduced to text at my direction; that said transcript is a true record of the proceedings therein referenced; that I am neither counsel for, related to, nor employed by any of the parties to the action in which these proceedings were taken; and, furthermore, that I am neither a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

/s/Carleton J. Anderson, III

Notary Public in and for the
Commonwealth of Virginia
Commission No. 351998
Expires: November 30, 2020