The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's
Patient-Focused Drug Development Initiative

Hereditary Angioedema

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Center for Biologics Evaluation and Research (CBER)
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Table of Contents

Introduction

On September 25, 2017, the FDA (or the Agency) held a public meeting to hear perspectives from patients with Hereditary Angioedema (HAE), their representatives, caregivers, and other stakeholders. The meeting enabled discussion of the impact of HAE on patients' daily lives and patient views on the currently available treatments as well as future product development. The FDA conducted this meeting as part of the Patient-Focused Drug Development (PFDD) Initiative, one of the Agency's commitments under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), to more systematically gather patient input on their medical condition and on available therapies. Under this initiative, the FDA has held 24 public meetings over the course of five years, each focused on a specific disease area. The meeting discussed in this report was the 24th and the concluding meeting of the PFDD initiative under PDUFA V. More information on this initiative can be found at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm.

Overview of Hereditary Angioedema

Hereditary Angioedema is a rare genetic disorder known to be inherited in the autosomal dominant pattern. The condition usually presents with recurrent attacks of severe swelling (angioedema) that may involve any part of the body and frequently affects mucosal surfaces such as the lining of the gastrointestinal tract, the mouth, the tongue, the throat, the larynx, the genitourinary system, and others. Attacks may also involve the face, arms, and legs, presenting at different locations and in an unpredictable manner. Symptoms of HAE range from mild to severe and, when severe, can result in hospitalizations or lead to the most serious, life-threatening complication: laryngeal edema.

Hereditary Angioedema affects approximately 1 in 50,000 people[1]; it is estimated that there are about 6500 individuals with this condition in the United States (U.S.). According to one study, HAE resulted in >5000 emergency department visits with 41% resulting in hospitalization[2] over a one year period in the U.S. The condition is known to be caused by genetic mutations on the SERPING1 gene and, although HAE is often inherited from at least one parent, it can also occur due to sporadic mutations appearing in this gene. SERPING1 gene controls the body's production of a protein called C1-Esterase Inhibitor. The C1-Esterase Inhibitor helps the body control inflammation and participates in the clotting cascade. Reduced amounts of C1-Esterase Inhibitor are associated with overproduction of plasma kallikrein and excessive release of a substance called bradykinin which can cause abrupt increases in vascular permeability leading to acute attacks of swelling in different parts of the body. Three types of HAE have been described: type 1 occurs in approximately 85% of patients and is associated with reduced blood levels of C1-Esterase Inhibitor; type 2 occurs in approximately 15% of patients and is associated

[1] https://ghr.nlm.nih.gov/condition/hereditary-angioedema#statistics.
[2] Zilberberg MD[1], Nathanson BH, Jacobsen T, Tillotson G. Descriptive epidemiology of hereditary angioedema emergency department visits in the United States, 2006-2007; Allergy Asthma Proc. 2011 Sep-Oct; 32(5):390-394.

with normal levels of a dysfunctional C1-Esterase Inhibitor; and type 3 occurs very rarely, is poorly understood, and has been reported in association with genetic mutations on Factor XII gene that encodes clotting Factor XII protein[3].

Symptoms of HAE typically begin in childhood, may worsen during puberty and perimenopause years, and continue throughout an individual's life. If untreated, attacks of swelling may occur, on average, every 1-2 weeks and may last from few to several days. Frequency and duration of attacks vary widely among individuals and may be associated with common triggers such as trauma, stress, infection, and exertion, or may occur without well-identified triggering factors. The symptomatology depends on attack location; hence, the gastrointestinal tract attacks present with abdominal pain, nausea, vomiting and diarrhea; the genitourinary tract attacks present with lower abdominal and groin pain, difficulty urinating, and genital swelling; and attacks involving the face and limbs present with disfiguring swelling and functional limitations of the involved parts. Attacks involving the oropharynx and larynx may present with voice hoarseness, noisy breathing, and shortness of breath and can lead to the most feared and life-threatening manifestation of HAE, laryngeal edema. When not treated appropriately in a timely manner, this complication may lead to suffocation and death. The laryngeal attacks are, therefore, considered to be the most urgent sequelae of HAE, and their treatment involves airway protection with urgent use of medications aimed to decrease laryngeal swelling, as well as intubation when needed.

The current therapies for HAE are generally grouped into the medications used to prevent attack occurrence (routine prophylaxis) and the medications used to treat an attack that has already started or is about to start. At the time of this meeting, there were seven medications approved by the FDA for the treatment or prophylaxis of HAE attacks. These medicines aim to decrease the inflammatory response and include mainly C1-Esterase Inhibitor replacement therapies and products that interfere with the kallikrein-bradykinin pathway. The following medicines are approved *for prophylaxis* of HAE attacks: Danazol® – oral androgen, Cinryze® – plasma-derived C1-Esterase Inhibitor for intravenous administration, and Haegarda® – plasma-derived C1-Esterase Inhibitor for subcutaneous administration. The following medicines are approved for the *treatment* of acute attacks of HAE: Berinert® – plasma-derived C1-Esterase Inhibitor for intravenous administration, Ruconest® – recombinant C1-Esterase Inhibitor for intravenous administration, Kalbitor® (Ecallantide) – plasma kallikrein inhibitor for subcutaneous administration, and Firazyr® (Icatibant) – bradykinin-receptor antagonist for subcutaneous administration.

Although the currently available treatments for routine prophylaxis of acute HAE attacks are effective in reducing the number and frequency of attacks, they do not eliminate all attacks in each individual. Similarly, the medications used for the treatment of HAE attacks are effective

[3] Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, Caballero T, Farkas H, Grumach A, Kaplan AP, Riedl MA, Triggiani M, Zanichelli A, Zuraw B; Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. Allergy. 2014 May; 69(5):602-616.

in reducing the time to improvement of the symptoms, but the attack resolution still requires time during which the patient remains symptomatic. Supportive treatments for HAE may also include medicines used to control pain.

Meeting Overview

During the meeting, the FDA had the opportunity to hear directly from patients, families, and caregivers about their experiences with HAE attacks and the life-changing impact of the available therapies. Approximately 110 patients with HAE and their representatives actively participated in the meeting in-person and 52 participants through the live webcast. Other meeting attendees included representatives from the FDA and other federal agencies, industry, as well as healthcare professionals and patient advocacy organizations.

Meeting discussions focused on two key topics: (1) disease symptoms and daily impacts that matter most to patients and caregivers, and (2) patients' perspectives on current approaches to treating HAE and on participating in clinical studies. The questions for discussion [Appendix 3] were published in a Federal Register Notice (82 FR 33503): https://www.federalregister.gov/documents/2017/07/20/2017-15202/patient-focused-drug-development-for-hereditary-angioedema-public-meeting-request-for-comments) prior to the meeting. For each topic, a panel of patients and patient representatives [Appendix 2] shared their comments to begin the dialogue. Panel comments were followed by a facilitated discussion inviting comments from other patients and patient representatives in the audience and online through the webcast. An FDA facilitator led the discussion, and a panel of FDA staff [Appendix 2] asked follow-up questions. Participants who joined the meeting via live webcast could submit comments throughout the discussion, and their comments were summarized during the meeting. In-person and webcast participants were invited to respond to polling questions [Appendix 3] and share their perspective on a given topic.

According to the participants' responses [Appendix 3, Questions 1-4], most patients partaking in the meeting in-person or via the webcast, were between ages 21 and 60 years old and lived in a city, town, or suburban area. While more participants in the room were women, the gender distribution was equal among the webcast participants. Overall, the responses to questions and comments of the polled participants generally reflected a wide range of symptoms and experiences with HAE.

To supplement the input gathered at the meeting, patients and others were encouraged to submit comments to a public docket[4], which was open until November 20, 2017. No comments were submitted through the public docket https://www.regulations.gov/docket?D=FDA-2017-N-3068.

More information on the meeting, including the archived webcast and transcript is available on the meeting webpage: https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm566079.htm.

[4] A docket is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov .

Report Overview and Key Themes

This report summarizes the input provided by patients and patient representatives at the meeting. To the extent possible, the terms used in this summary to describe specific manifestations of HAE, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire HAE patient population or any specific group of individuals or entities. There may be symptoms, impacts, or treatment experiences that are not mentioned in this report.

The input that the FDA received from this meeting highlights the diversity of HAE manifestations, the range of issues that accompany HAE, and the challenges that patients and their families face in dealing with this condition. Several key themes discussed throughout the meeting are summarized below.

- The meeting participants spoke about years of diagnostic delays and the fact that the recognition of symptoms and signs of such a rare disease as HAE remains limited on the part of physicians and other healthcare providers. The patients and families described the ongoing struggles with explaining their symptoms and convincing emergency room personnel to give them appropriate treatments. They also described the consequences of misdiagnosis and misunderstanding of HAE, including unnecessary surgical interventions, prolonged hospitalizations, insufficient treatment of pain, and the overall poor health outcomes related to the lack of understanding of their disorder. One common theme that transpired throughout the discussion was the importance of building awareness and education about HAE and its treatments in the healthcare community.

- The meeting participants referred to the unpredictability of attack occurrence and emphasized that not knowing when an attack will occur and which part of the body it will involve is one of the most difficult aspects of HAE that makes the biggest impact on the lives of patients and their families. They bravely and honestly described the associated stress, anxiety, and depression that accompany attack occurrence and the fear of developing, or seeing their loved ones developing, the most devastating and life-threatening manifestation of HAE: laryngeal edema.

- Both affected and unaffected members of families with HAE described the attacks that involve different body parts including severe and often excruciatingly painful abdominal attacks, disfiguring facial edema referred to as “monster effect” by HAE community, disabling and mobility-limiting swellings involving hands and feet, intolerable urinary symptoms, and other effects of the condition. Many participants talked about either experiencing or seeing their loved ones experiencing life-threatening laryngeal swellings and the effects of endotracheal intubation and tracheostomy placements.

- The meeting participants discussed the emotional toll that HAE has had on them, the fear of passing the disease to their children, and stress, anxiety, fatigue, and depression that accompany this condition. They described frequent challenges with school and work attendance, constrained social interactions, disrupted family life, and limitations of

participation in sports and other activities. Both patients and family members reflected on the necessity to infuse or inject medications at home and to have timely access to medical facilities to be able to effectively treat attacks in a timely manner.

- Several participants described the known triggers for their attacks but also expressed that many attacks may occur without any specific harbingers. This anticipation of a possible attack often leads to patient hesitancy to receive appropriate preventive care (gynecological exams, mammograms) and dental care because these procedures may result in mild mechanical trauma or pressure to the mucosal surfaces and soft tissues with a potential to trigger an attack. Several women with HAE described worsening of attack frequency and severity during puberty and the perimenopause years, and suggested additional research to be conducted to evaluate the impact of hormonal changes on HAE disease course.

- Throughout the discussion, many participants commented on the life-changing experience with the availability of the new treatments developed and approved for HAE in recent years. Both patients and physicians participating in the meeting have acknowledged the dramatic change in the disease course and health outcomes brought about by the treatments targeting C1-Esterase Inhibitor and kallikrein-bradykinin pathway. In addition to the tremendously positive effects of the available therapies, many participants stressed that the known side effects of the parenteral administration and the use of chronic intravenous catheters are not without the risks of infection, thrombosis, additional need for surgical interventions related to catheter placements, and awkward physical appearance.

- Many participants expressed the opinion that there still exists an unmet need for new treatments that are less invasive, improve predictability of attacks, have fewer side effects, and ultimately lead to a cure. In addition to commenting on the need for more research related to hormonal influences on the disease, the meeting participants emphasized the importance of studying effects of new therapies in children and in those people who have HAE types and/or patterns that may be less responsive to the currently available therapies. Many discussants expressed their willingness to participate in clinical trials and all participants polled in the room indicated that they would want to be part of a natural history study for monitoring their disease course and effects of treatments.

Topic 1: Disease Symptoms and Daily Impacts That Matter Most

The first topic of discussion at the meeting focused on patients' symptoms. FDA asked participants to discuss HAE attacks presenting at different body locations and how these attacks impact patients' daily lives. Five panelists provided comments to start the dialogue. They included a brother of a 7-year-old girl with HAE who experienced abdominal, laryngeal, facial, and extremity attacks, and 4 adults of different ages [Appendix 2] whose symptoms started during childhood and/or adolescence and continued into their adult lives. These participants described their struggles with initially inexplicable and unpredictable symptoms, years of waiting

for the correct diagnosis, unnecessary surgical interventions, and general misunderstanding of their condition on the part of others, including healthcare professionals. The panelists described the attacks and symptoms they had had at the time when no HAE treatments were available except for anabolic steroids. They emphasized the life-changing experience they had with the new treatments targeting C1-Esterase Inhibitor and the kallikrein-bradykinin pathway after these medicines had been approved and become available on the market. The panelists also shared the significant fears, frustrations, and stresses as well as school, job, and relationship losses that they and their loved ones had suffered due to HAE. Their testimonies started the dialogue which continued over the course of the meeting, and nearly all patients and patient representatives in the audience indicated (by a show of hands) that their or their loved one's experiences were reflected in these panelists' stories.

Perspectives on Symptoms

Time to Diagnosis

When queried on the amount of time that patients had to wait until their condition was appropriately recognized and treated, 54% of the participants present in the room and 40% of the webcast participants [Appendix 3, Question 5] reported that it took 10 years or greater for them to receive the correct diagnosis.

One participant described her experience as follows, "I waited 16 years for a diagnosis… in one year I was admitted in the hospital for 184 days…"

Two other participants summarized the collective HAE community's experience with delays in the diagnosis by saying, "That is something that, I think, we all share… is going to the hospital, especially when it is new and you don't know what it is, and being completely misdiagnosed." and "Everybody has a story of a doctor telling them to take Benadryl and wait."

Several participants commented on the general need to improve the recognition of HAE by the healthcare system and, particularly, by emergency departments, paramedics, and practicing physicians. Participants commented that additional educational efforts for healthcare providers through various venues will be important in improving the recognition of and providing timely and appropriate treatments to patients with HAE.

Abdominal Manifestations

Many meeting participants described and discussed the devastating symptoms of severe abdominal pain, swelling, and accumulation of intra-abdominal fluid, nausea, vomiting and diarrhea that occur during abdominal attacks of HAE. The abdominal pain, nausea and vomiting were reported by the in-person meeting participants as the first (27%) and the third (15%) most frequent symptoms that had the greatest impact on their lives [Appendix 3, Question 6].

These symptoms were vividly described by one participant, "I have birthed two babies without epidurals and I have actually had a kidney stone, so I do have a high tolerance for pain…. and

this pain [HAE abdominal attack] is above 10 on the pain scale…During these attacks, I can't eat, I can't drink, you basically vomit every little bit that is in you…"

Laryngeal Manifestations

Almost all of the participants who spoke during the meeting commented on the tremendous impact of the throat swelling (laryngeal edema) that may occur with HAE. This life-threatening manifestation was cited as the most feared complication of the condition. Whether witnessed in a family member, experienced first-hand, feared before going to sleep, or survived after intubation and mechanical ventilation, this manifestation was described by the participants as, undoubtedly, the most traumatic experience of HAE. Hoarseness, throat swelling, or difficulty breathing were cited as the second most impactful set of symptoms [Appendix 3, Question 6] among the in-person participants (24%) and as the first most impactful set of symptoms among the webcast participants (75%). When queried about experiencing one or more attacks involving the throat or the larynx, 89% of the in-person participants and 75% of the webcast participants answered positively with 29% in-person and 25% online participants saying that they had to be intubated to treat the attacks [Appendix 3, Questions 7, 8]. Shown below are some of the testimonies shared by patients, their family members and caregivers:

"All types of HAE swelling can be uniquely disabling. Laryngeal swelling has always been my and every HAE patient's worst fear... This fear is something that we think about every day and often the last thing that we think about at night."

"My stepfather was previously intubated after suffering a throat attack and the thought of that happening to my little sister is agonizing."

"I have been intubated three times. The very first time they had to resuscitate me because they had trouble getting the tube down. I stayed in the medical ICU[5] for three days…"

"…There is 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 are waiting to get to the emergency room."

Facial Manifestations

Several participants discussed how facial swellings affect patients with HAE, particularly children, who may feel as if they look like "a monster". The brother of a girl who has experienced facial swelling asked his sister what matters most to her and described her answer as follows: "…when my face swells up, it makes me look like a monster and I am not pretty." Commenting later about the emotional toll related to HAE, the same participant said, "…I worry that she will never be able to see herself as beautiful…"

Several participants commented about the "monster effect" and the inability to go to school or work, or to participate in any social activities due to the facial appearance. One mother described her young son, "… his face would be just swollen enough on one side to make him

[5] Intensive Care Unit.

look disfigured. He'd look at me and say "I can't go to school—I look like a monster …and he was just in kindergarten."

Swelling Involving Arms and Legs

Participants who have experienced HAE attacks involving arms, hands, legs, and feet shared their experiences. As an example, one participant said "…if the bottoms of your feet are swollen, you cannot walk anywhere. And if your hands swell up like a balloon… you cannot pick stuff up, you cannot pull up your pants… you cannot do anything, dress yourself, feed yourself... When both your hands and your feet are swollen, you cannot do anything except just sit there."

Two other people mentioned the impact of the hand swelling on their work and daily life.

"I had to quit my job because I could not hold anything. My hands would swell up too much… and working at a fast food restaurant, you need your hands for every aspect."

"Yesterday I stopped by [a shop] and this morning my hands swelled from carrying all of my purchases in a plastic bag."

Urinary Manifestations

When asked to participate in the poll about additional symptoms affecting their lives, 7% of the in-person participants indicated urinary symptoms and inability to urinate. One participant shared a very traumatic experience of catheter insertion and another shared her perspective on the effects of HAE.

"…Anything is a disruption in your day, even if they just say seven percent of [people referring to difficulties with] going to the bathroom. Everybody knows how profound that is when you cannot go to the bathroom, in that moment it is hundred percent."

Anxiety, Depression, and Fatigue

Anxiety and depression were mentioned by many people as significant symptoms having serious impact on their lives. Several participants gave their testimonies in explaining how these symptoms affect their emotional health.

"Through all this [HAE], the other most debilitating symptom is mental health… I suffer with depression; I suffer with anxiety."

"Fatigue has followed me everywhere since I was 14, and I did not have the energy to go out…so I have no friends…"

"I think 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 do not even know what to expect… you do not know what is going to make you swell."

"This [HAE] has affected my entire life. It is like I have been diseased emotionally as well, because of all the things that this [HAE] has impacted in my life.

A family member of a young patient shared "The unpredictable nature of this disease makes it difficult for Katie and for our family to live without fear and without worry."

Pain and Labeling of "drug-seeking"

All meeting participants recognized that pain almost always accompanies swelling, regardless of the attack location. Several participants described their pain, and one summarized the problem of being accused of seeking pain drugs as a common issue frequently encountered by HAE community.

"I became familiar with pain from a very young age."

"…In the sixth grade I missed 65-70 days of school due to stomach pains. They would be so bad… I would just crunch over. When it first started, the doctor gave me phenobarbital; then another time next year I was on Librium; next year Diazepam or Valium, and the pain just continued, continued, continued…"

"My worst attack was in my sophomore year of high school… I had a nineteen-day attack with no relief, no pain medication… I was just lying in bed in pain for almost a month…"

"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 are often labeled as drug seekers."

Hormonal Influences

An emerging topic that was expressed by several participants of different ages concerned the role of changes in the hormonal background that occur at different ages and affect women.

One participant described it as follows, "I had my first severe abdominal swell as a grown person… I had started taking birth control pills like many young girls not knowing that that was going to be a trigger for an abdominal swell."

Another participant echoed from a different age but with a similar perspective "I am going through the menopause right now… Since September I had 10 attacks [of HAE], three in my throat, three in my face, and other parts of my body…"

Yet another participant expressed "One issue that is very common for women is that the disease is often triggered by hormonal changes. When you are in your teens, you often have your first 'really bad' episodes… For me, [it was] pregnancy… I went through four pregnancies extremely sick…I would like to see a lot more research about the hormonal impacts and how you can adjust medications and things based on where you are in your life hormonally… all those different aspects of your life as a woman that severely affect the disease."

Attack Triggers

A common theme expressed by many participants was discussion of the factors that trigger HAE attacks. One of the FDA panelists asked the meeting participants to describe any triggering events that they had experienced before HAE attacks. Some of the triggers that were described are below.

"When I was in college, I ran track and cross-country, and sometimes hard workouts and races would trigger the abdominal events."

"If I go swimming, snorkeling… the mask would cause my face to swell."

"I am going to be a little brave here, physical intimacy is also affected… it is hard to have a relationship with your partner for fear of swelling."

Other participants named stress, anxiety, changes in barometric pressure, soft tissue trauma, viral infections, salty and acidic foods, repetitive motion of walking or exercising and emotional excitement of feeling happy as triggers that they or their loved ones had experienced.

Several participants commented on triggers that are part of the medical preventive care, such as dental work, Papanicolaou (Pap) smear, and mammogram which may occasionally induce attacks because of applying mechanical pressure to soft tissues and mucosal surfaces. One participant discussed that forgoing the routine preventive care and sometimes medical and dental care for the fear of triggering attacks is one common issue with HAE; his comments were supported by others who had similar concerns.

"People forgo necessary medical treatment because they are afraid that it would trigger [an] HAE attack. One of the things is dental work…they are terrified to get the necessary dental work done because they are afraid it is going to trigger a laryngeal attack."

Hospitalizations

Hospitalizations were mentioned by most meeting participants, and 95% of the in-person participants responded that they, or their loved ones, had to be hospitalized because of HAE attacks [Appendix 3, Question 9]. Approximately 38% of the respondents were hospitalized once and 62% or more of the in-person and webcast participants were hospitalized two or more times [Appendix 3, Question 10]. Several participants noted that such statistics were reflective of what had happened to people over their life time and not in the previous year (as was asked in the polling question) because one of the positive effects of the recently approved C1-Esterase Inhibitor targeting therapies was the reduction in rates of hospitalizations resulting from successful attack prevention and early treatment. When speaking about hospitalizations, many participants referred to the "dark ages" when no treatments were available except for anabolic steroids.

One participant recalled their experience, "I went on to have a number of different hospitalizations primarily for airway events and during that time I was intubated 6 times."

Another commented, "…because of all of the work we have done together [advocacy for disease treatments and products development and approval], our lives have improved so much in the last five years that Question 9 [the question about hospitalizations] does not apply to my life anymore, and I am grateful for that."

Perspectives on the Overall Impact of HAE on Daily Life

Many meeting participants commented that HAE attacks lead to various limitations in their daily activities including inability to go to work, to school, participate in sports, social activities, take care of themselves, their children, and family members. They also spoke about feeling anxious and left out of life activities [Appendix 3, Question 11].

Unpredictability

Participants described the stress caused by the unpredictability of the disease. One person explained, "One of the toughest things in HAE is the unknown… can swell without warning and for what seems no reason at all."

Another participant said, "And 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."

Employment

Several meeting participants discussed the limitations that HAE have put on the availability of jobs and career choices. One person described how she could get through college and find a job despite being discouraged by others. Other examples of comments included those related to limitations on the job and job losses.

"I have lost 14 jobs because of this disease."

"Any time I had an attack, I would lose three to four days out of work, out of life, would be in and out of hospitals. I remember those days [and being] curled up in my bed, waiting for an attack to end…"

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

Missing School, Sports, and Other Activities

Several participants told about the difficulty they or their loved ones had in attending school and not living up to their potential.

"Much of the disease for me has been about not being able to live out to my potential. I missed a ton of school…"

"When I was in my senior year of high school, I was homeschooled for six months…"

One participant shared about his family member, "…she does miss more than healthy kids her age do… she missed school, sports games, holidays, and play dates because of swelling."

Another person mentioned limitations of participating in her favorite sport, "I was involved in competitive dance… when I finally got on the treatment plan and got in college, I tried out for the dance team and made it and practiced with them. After that, the team physician told me that I could not participate because I was a liability to the university."

Family Life

A common topic expressed by many meeting participants was the effect that HAE can have on the daily life of a patient's family as well as family relationships and family planning. Participants spoke about the restrictions that they have in any activity of daily life and family life and feeling of guilt for knowing what their families must go through because of their condition. Several examples of the concerns and worries shared by the participants are shown below.

"I have missed out a lot and my family missed out a lot because of me."

"There is another piece to this…people fear passing the gene onto their family members. As a result, some folks may be hesitant to have children and that is something we have heard quite a bit in the anxiety spectrum."

"…Another thing I carry as a parent is guilt because now it is my babies [affected]."

"As a parent that has children with HAE, you… live in absolute dread of the next attack."

Social Life

Many participants described how HAE affected their interactions with others and their planning for activities in life. Some examples are shown below.

"Planning things is like 50/50 chance… It impacts relationships, it harmed friendships that I had, you know, people were wondering why I always cancelled out on them."

"On a day-to-day basis, I have no social life because I have lost friends who think that I just want to blow them off. I don't… I want to go out… I cannot because I am either in excruciating amount of pain or I have fatigue…"

"It [HAE] limits your life when you are having an attack and when you are not having an attack…the anxiety is real and a lot of people feel that way. It [HAE] definitely affects all aspects of your life."

Topic 2: Patient Perspectives on Current Approaches to Treatments

The second main topic of discussion focused on patients' experiences with therapies used to treat their or their loved ones' condition and participation in clinical studies. Five panelists provided comments to start the dialogue [Appendix 2]. The panelists shared their experiences both before and after the new therapies targeting C1-Esterase Inhibitor and the kallikrein-bradykinin pathway became available.

Perspectives on Current Treatments of HAE

Life-Changing Effects of Available Therapies

Many meeting participants shared their perspective on the truly life-changing experiences they had with initiating treatments that have been approved for HAE since 2008. Some of the comments made by the participants are shown below.

"Thankfully, I have been on a new treatment and it has greatly affected my life. And just to compare the difference, I can live life without worry of an HAE attack, I can go to college (I am in nursing school), and I am living and working and being a good mom and a wife that I never thought was possible."

"I never thought I would graduate from high school and move on to college but, fortunately, I was able to get on a treatment plan and it seemed to keep me pretty well controlled."

"When people ask me how you have lived with HAE, it is like two different worlds. There is one before therapy and one after."

"The current treatment has changed my life drastically. Back in the day when I was first diagnosed, there was nothing, and then there was Danazol… [steroids]… going on those therapies for 30 years I had a heart attack when I was 45 years old. So, I am really happy to see the therapies that we have now. Today's modern therapies are wonderful and life-changing, as you have heard already many times today."

"One would look at my children and see two beautiful adults now… they are both married, they are parents, they are productive, and they work all over the world. Their therapies have changed their lives… have given them security, have given them freedom, and we are so grateful."

Use of Medicines for Attack Prophylaxis

During the meeting, the participants discussed therapies that they use for prophylaxis of HAE attacks. One of the polling questions referred to the use of medications for routine prophylaxis of HAE attacks. Most participants in the room and online noted that they use Cinryze and Haegarda [Appendix 3, Question 12]. A small percentage of people reported using Danazol. About 39% of the in-person poll respondents and 75% of the webcast respondents chose "other" as their option for prophylactic treatment. Upon facilitated questioning, several people explained that they participated in clinical trials with new treatments; one participant said that she used a medicine that had been approved for the treatment of HAE as an off-label treatment for prophylaxis of her attacks.

Use of Medicines for Attack Treatment

When discussing treatment options and answering the question about the therapies used for the treatment of HAE attacks, most in-person and online respondents chose Firazyr followed by C1-Esterase Inhibitors Ruconest and Berinert, followed by Kalbitor [Appendix 3, Question 13]. Three percent of the in-person meeting participants and poll respondents chose "other" used for the treatment of attacks. One parent of an adult patient commented: "A lot of women have mentioned the role of hormones. My daughter chose progesterone-only therapy when no therapy approved by the FDA was available. This treatment works for her."

Time of Treatment Initiation

The time of treatment initiation upon attack occurrence was also discussed. About 43% of in-person participants indicated that they would treat once pain or discomfort from swelling becomes intolerable and 33% reported treatment initiation when no symptoms have appeared yet, but the person may start feeling an attack coming on [Appendix 3, Question 14]. For the webcast participants, the responses went in the opposite direction, with 62% choosing to initiate treatment when no symptoms have appeared yet and 25% when pain or discomfort from swelling becomes intolerable. Some of the comments from the meeting participants explaining their choices are shown below.

"Over the years, I have learned that effective treatment is to get it right away when the attack starts. Because if I do not, then I am already in pain, the swelling has already started, and it takes longer to resolve."

"I want to say as a patient, it is really important to treat early… you are going to feel a lot better sooner. I am not sure how a lot of people are, but I know for me it is never just my hand. And you never know-- it could travel to various places, abdominal, even laryngeal. It is just really important to treat every attack as soon as possible."

One participant reflected on the responses from the audience "I think something that is really important… is that we wait until there is pain or the discomfort is intolerable…a lot of times I convince myself that maybe it is not an attack until it becomes intolerable… So, I think 43% sort of holds that true to a lot [of us] … like we can say, oh, maybe I have a cold or maybe it is just a

headache, or maybe I just do not feel great this morning. And then four hours later, we are in that intolerable discomfort. I have heard people say that they wait too long because they think maybe it is not necessarily [an attack] although they know exactly what it really is."

About 12-13% of respondents indicated that they use treatment only for throat or facial symptoms. This is one explanation that was provided, "I was told by my doctors…because I take an acute therapy [on demand] … that if I have swelling in my face or my throat, to take the medication right away but not to take it for my hands or my feet."

One of the FDA panelists asked to give examples of the warning symptoms that may precede an attack of HAE. Some of the symptoms and signs that were named by both in-person and webcast participants included: rash, extreme fatigue, headache, dizziness, lightheadedness, feeling tightness or achiness in the hand or foot that is about to swell, abdominal cramping and burps, bad breath, facial tingling and itching, eye redness, and feeling irritable and short-tempered.

Meaningful Treatment Effects and Choice of Treatments

The meeting participants then discussed which benefits they would consider the most meaningful for the treatment of their condition. The distribution of responses showed that the reduction in attack frequency was chosen most often by both the in-person and the webcast participants (36% and 75%, respectively). However, it became clear from the ensuing discussion that all the listed effects, including the reduction in attack severity and the rapidity and completeness of the treatment response were considered meaningful and important by the respondents.

The participants were asked to rank and comment on the factors that they would consider most important in making their decision regarding which treatment they would prefer (of those currently available as well as developed in the future). The most frequently chosen factor was the route of treatment administration, often reflecting the need for less traumatic administration (oral more preferred than subcutaneous, subcutaneous more preferred than intravenous). This proceeded then to a discussion related to traumatic, thrombotic, infectious, and emotional complications of the intravenously inserted portal catheters. The frequency of administration and access to treatment (e.g., insurance coverage, cost, regional availability) were other important factors cited by the respondents as influencing their choice of treatment. Overall, 12% of the respondents indicated that infrequent but serious and severe side effects would be important for their treatment consideration, and 7-12% indicated that they would be concerned about common and non-severe side effects of the medications. Some of the comments from the participants are cited below.

"I am concerned about long-term effects of medications. I am 25 years old now… if I am still taking this medicine through the next 50 years, what are the side effects going to be?"

"I had a portable catheter implanted [for treatment]. That port malfunctioned and had to be taken out. I had a PICC[6] line implanted, that PICC line came out. I am now on my second portable catheter…" The same participant continued "…one thing that could happen is development of

[6] Peripherally Inserted Central Catheter.

blood clots…but I think trying to be aware of the method of how a medication is administered [is important] … Obviously having a pill a day would be fantastic… subcutaneous [method of administration] is a nice compromise… so I guess trying to be aware of other things that go into the method of treatment."

There were several comments made about the availability of treatments and the need to provide additional information to the third-party payers. One patient participant commented: "…Say, you are supposed to be able to take three doses per day and your insurance says, well, I am going to give you only three boxes a month. What do we do then for the other 20 days… have an attack…? So, sometimes the option of access to treatment is taken out of our hands."

One physician participant commented: "I am a physician… I take care of a large group of patients with HAE. I have had patients that have not had their medicines filled because, for example, they have to prove they have HAE. I have blood work from several years ago that proves they have HAE, but I will get calls from the insurance company saying that they need recent blood work. Well, this is a genetic disease, it does not change. So, patients have lapse in their therapy which is not good for them and extremely frustrating for me..."

Unmet Needs for More Treatment Options

Throughout the meeting, the participants returned to the theme of additional treatments and the remaining unmet needs for development of new products for HAE. They provided a range of perspectives which included:

- Developing new treatments that have less traumatic routes of administration;
- Approaching development of new therapies through other pathogenic mechanisms, including recognition of hormonal changes;
- Finding better treatment options for patients who have HAE Type 2 and have a dysfunctional C1-Esterase Inhibitor present at normal levels;
- Expanding on research and clinical studies focused on product development for children with HAE;
- Developing products that work longer and make the HAE course and attack appearance more predictable; and
- Finding treatments that can ultimately provide a cure.

Some excerpts from the meeting participants' comments are shown below.

"I feel that as a community we have 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 do not 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..."

"HAE patients, in general, need more treatment options and easier access to medications."

"It is very crucial that the FDA continue to fund our research because, for me, the type I have [patient who has HAE with normal C1-Esterase Inhibitor] 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 will not be able to respond in time for…"

"It is 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 that I have a tube hanging out of my arm is really sort of an awkward conversation to have."

"We finally got the diagnosis, so I would like to see a lot more research about the hormonal changes, and how you can adjust the 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."

"In a perfect world, longer lasting therapies would help me live as if I did not have HAE at all. The therapy that could soon ward off attacks for long periods of time would allow me to almost forget that I have HAE. Therapies 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 does not have me."

"I remember a couple of months ago she [my daughter] 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 and could not get one so I started calling urgent care centers 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 to how to treat HAE. The two or three urgent cares near our house pretty much refused our request for help. They said I could not bring the medication in. They just did not feel comfortable giving her the medication. I called a couple of emergency rooms and I was not getting a definite answer whether they would do it or not. Thankfully, that night I was able to infuse her…. but I still have concerns over the next time she has an attack and I cannot get vein access for her. I just want to stress the idea that we still do need better medications…"

During the discussion, the President of the Hereditary Angioedema Association (HAEA) [Mr. Anthony Castaldo] summarized some informative research conducted by the Hereditary Angioedema Association through their existing patient registry. The results of this research reflected the need for finding additional therapies to better control HAE attacks.

"If you look at some of the studies that we do, we are not quite there yet. We actually did a study of 980 patients not too long ago. Seventy four percent (74%) of the patients that we polled in our 980 patients sample said they had more than one attack a month. Fifty percent (50%) said they were not satisfied with their available therapy… 50% of the participants said they had used or were currently using an indwelling port… it is important that we understand that there cannot be any complacency… we still have a need for better therapies and, ultimately, for a cure."

Perspectives on Participating in Clinical Trials

The FDA was particularly interested in hearing patients' and families' perspectives on participating in clinical trials investigating new treatments for HAE. In response to the polling question asking about trial participation [Appendix 3, Question 17], the overwhelming majority of people said they would be willing to participate in clinical trials, with about one third saying that their participation would depend on various factors. When asked to discuss these factors, the participants primarily talked about the difficulty with taking placebo given the unpredictability of the course of HAE and a possibility that the next attack may result in laryngeal edema putting patients in a life-threatening situation.

The following examples illustrate the perspectives shared. "I participated in one of the clinical trials… I, unfortunately, got the saline and had to drop out… because I would have ended up in the hospital because almost every day I was attacking [having attacks]. So, there has to be some way to allow people to know that they can escape and get the real drug or [be treated] open-label if it [investigational treatment] is not working for you…"

"Back in 2005 I reached a low end and was willing to do anything… and a trial with Cinryze opened up… Cinryze changed my life absolutely. I have been on it ever since and, over the years, have been asked by various people if I would be willing to become part of another trial… I would have had to give up Cinryze. I was not willing to do that… I finally had the quality of life and was not going to give up a known for an unknown."

One participant noted that it was important for him to participate in clinical trials and contribute to obtaining more knowledge about HAE to find better treatments for his children.

In response to the polling question related to the reasons that may influence people's decisions about trial participation, 53% of the in-person participants and 100% of the webcast participants indicated that, although their condition was well controlled, they would be willing to participate in a new trial if they could receive proper treatment with an FDA-approved product for acute attacks that might occur. About 25% of the in-person and 62% of the webcast participants indicated that their treatment did not work as well as they would like it to work [Appendix 3, Question 18].

The meeting participants were also asked to opine on whether they would agree to participate in clinical trials if the treatment has a potential to result in a cure but might carry a small risk of serious side effects including cancer. The clear majority of the in-person meeting participants chose the negative answer (72%). At the same time, 12% of the webcast participants chose the negative answer and mostly expressed hesitancy reflected in 62% of people choosing a tentative "maybe" option [Appendix 3, Question 19]. There was a short discussion of the responses and one participant expressed their opinion by saying, "…Would you be willing to take on the risk of getting cancer? …If it is 5% risk, no. But if it is half of a percent, maybe I would…"

Finally, all respondents to the meeting polling questions indicated that they would be willing to participate in a study in which the course, or the natural history, of HAE and its treatment were monitored and assessed over time, but in which patients would not receive any specific new

treatment as part of the study [Appendix 3, Question 20]. One of the members of the HAEA spoke about the registry that HAEA has initiated, and emphasized the value of having such registry to monitor the disease history and to trace the effects of the available and new medications on the disease as well as on patients' quality of life.

Summary of Public Comment: Testimonies from Four Physicians

Four physicians who routinely take care of patients with Hereditary Angioedema and who have had long-term experience with treating this condition spoke during the Public Comment period. All four speakers acknowledged the tremendous progress that has been made in this field, the role of patient advocacy, and the efforts of the larger community of stakeholders who helped to develop treatments for HAE. In their comments, they outlined additional needs to be addressed and offered future directions for advancements in the field. The main points of their comments are summarized below.

- Importance of continuing to consider new and better trial designs to meet the needs of HAE patients. Given that the use of placebo is not acceptable in this patient population, consideration should be given to the use of historical data and cross-over designs where all patients can receive investigational or standard-of-care treatment;
- Urgency to develop better product formulations that can be given "easily and conveniently without the use of injections." Several people commented on this same issue throughout the meeting discussion;
- Demand to pursue development of treatments that can improve predictability of HAE attack occurrence or eliminate attacks completely;
- Need for additional clinical studies to understand the variability of individual treatment responses, including pharmacogenomic and other studies that may help determine each person's disease course and response to treatment;
- Call to develop more treatment options for children with HAE, including for both treatment and prophylaxis of HAE attacks;
- Necessity for educating healthcare providers and other participants of the healthcare system about HAE and the momentousness of continuous effort by multiple stakeholders in helping families find experienced physicians and facilitate new product development.

One of the physicians who spoke during the period of Public Comment concluded the discussed themes as follows, "I think any attack has to be treated as a serious problem and should be recognized as such. And, as you think about the need for new and effective drugs, we need to get people to the point where we [they] are not having attacks at all, before we can say that we have reached where we want to go."

Conclusion

This Patient-Focused Drug Development meeting gave FDA and other stakeholders a rare opportunity to hear directly from patients, families, and caregivers about their past and current experiences with HAE, the issues related to the recognition, diagnosis, and management of this disease, and what people with HAE would like to see in the future to allow them to lead normal, fulfilling lives.

FDA shares the patient community's commitment and desire to advance the development of safe and effective therapies for patients with HAE. The perspectives communicated at this meeting have strengthened our understanding of challenges faced by those who live with this condition. The many patients' testimonies will serve to inform the development of new therapies for this disease. The Agency is tremendously grateful to those who participated in this meeting and took the time and effort to present their views and share their personal experiences.

Appendix 1: Meeting Agenda and Discussion Questions

Patient-Focused Drug Development Meeting on Hereditary Angioedema
September 25, 2017

Time	Description
8:00 – 9:00 a.m.	**Registration**
9:00 – 9:10 a.m.	**Welcome and Introductions** Larissa Lapteva, M.D. *Associate Director, Division of Clinical Evaluation, Pharmacology and Toxicology (DCEPT), Office of Tissues and Advanced Therapies (OTAT)* Donna Lipscomb *Director, Division of Manufacturers Assistance and Training (DMAT), Office of Communication, Outreach and Development (OCOD)* *Center for Biologics Evaluation and Research (CBER), FDA*
9:10 – 9:20 a.m.	**Opening Remarks** Wilson Bryan, M.D. *Director, Office of Tissues and Advanced Therapies (OTAT)* *Center for Biologics Evaluation and Research (CBER), FDA*
9:20 – 9:30 a.m.	**Overview of FDA's Patient-Focused Drug Development Initiative** Theresa Mullin, Ph.D. *Director, Office of Strategic Programs* *Center for Drug Evaluation and Research (CDER), FDA*
9:30 – 9:50 a.m.	**Background on Hereditary Angioedema and Therapeutic Options** L. Ross Pierce, M.D. *Medical Officer, DCEPT, OTAT, CBER, FDA*
9:50 – 10:00 a.m.	**Overview of Discussion Format** Donna Lipscomb *DMAT, OCOD, CBER, FDA*
Topic 1: Effects of Hereditary Angioedema that matter most to patients and caregivers	
10:00 – 10:30 a.m.	**Panel Discussion on Topic 1** A panel of patients and patient representatives will provide comments followed by a facilitated group discussion with participants from the audience.
10:30 – 11:30 a.m.	**Facilitated Group Discussion on Topic 1** Patients and patient representatives from the audience will be invited to contribute to the discussion.
11:30 – 12:30 p.m.	**Lunch**
12:30 – 12:35 p.m.	**Afternoon Welcome** Donna Lipscomb *OCOD, CBER, FDA*
Topic 2: Patients' perspectives on current treatments	
12:35 – 1:05 p.m.	**Panel Discussion on Topic 2** A panel of patients and patient representatives will provide comments followed by a facilitated group discussion with participants from the audience.

Time	Description
1:05 – 1:45 p.m.	**Facilitated Group Discussion on Topic 2** Patients and patient representatives from the audience will be invited to contribute to the discussion.
Topic 3: Patients' perspectives on participation in clinical studies	
1:45 – 2:15 p.m.	**Facilitated Group Discussion on Topic 3** Patients and patient representatives from the audience will be invited to contribute to the discussion.
2:15 – 2:45 p.m.	**Open Public Comment**
2:45 – 3:00 p.m.	**Closing Remarks** Larissa Lapteva, M.D. *Associate Director, DCEPT, OTAT, CBER*

Appendix 2: FDA and Patient Panel Participants

FDA Panelists

Theresa Mullin	Office of Strategic Programs, CDER
Diane Maloney	Office of the Director, CBER
Jonathan Goldsmith	Rare Diseases Program, Office of New Drugs (OND), CDER
Meghana Chalasani	Office of Strategic Programs, CDER
Christine Mueller	Office of Orphan Products Development, Office of Commissioner
Stacy Chin	Division of Pulmonary, Allergy, and Rheumatology Products, OND, CDER
Tejashri Purohit-Sheth	Division of Clinical Evaluation and Pharmacology/Toxicology, OTAT, CBER
Sara Eggers	Office of Strategic Programs, CDER
Larissa Lapteva	Division of Clinical Evaluation and Pharmacology/Toxicology, OTAT, CBER

Patient Panelists

Topic 1

Michael Ardito
Shari Starr
Doug Selsor
Kelsie Neahring
John Williamson

Topic 2

Lois Perry
Joyce Wilmot
Janet Long
Karen Dorsett Baird
Anthony Castaldo

Appendix 3: Meeting Polling Questions

The following questions were posed to the in-person and webcast meeting participants at various points throughout the meeting on September 25, 2017. Participation in the polling questions was voluntary. The results were used as a discussion aid only and should not be considered as scientific data.

Questions	FDA campus (in-person)	Remotely (through webcast)
1) Where do you live?		
A. City	36%	44%
B. Town or suburban area	51%	44%
C. Rural location	13%	11%
2) Have you, or your loved one, been diagnosed with Hereditary Angioedema?		
A. Yes	98%	25%
B. No	2%	75%
3) Are you?		
A. Female	77%	50%
B. Male	23%	50%
4) What is your age in years?		
A. 20 or younger	9%	0%
B. 21-40	24%	50%
C. 41-60	50%	42%
D. 61 or greater	17%	7%

5) How many years elapsed between the time when you experienced your first symptom and the time when you were diagnosed with Hereditary Angioedema?		
A. Less than 1 year	20%	0%
B. 1 or more but less than 3 years	11%	60%
C. 3 or more but less than 5 years	6%	0%
D. 5 or more but less than 10 years	9%	0%
E. More than 10 years	54%	40%
6) Of all the symptoms that you have experienced with Hereditary Angioedema, which ones have had the most significant impact on your life? Choose up to three.		
A. Hoarseness, throat swelling, or difficulty breathing	23%	75%
B. Abdominal pain	27%	0%
C. Swelling of the face	14%	50%
D. Swelling of the arm/hand or leg/foot	6%	0%
E. Swelling of the tongue	1%	50%
F. Nausea/vomiting	15%	0%
G. Difficulty urinating or genital swelling	7%	0%
H. Other symptoms not listed	6%	25%
7) Have you experienced one or more attacks involving your throat or larynx (windpipe)?		
A. Yes	89%	75%
B. No	11%	25%
8) If you answered "Yes" to the previous question, was a breathing tube inserted into your windpipe?		
A. Yes	29%	25%
B. No	71%	75%

9) Have you ever had an attack of Hereditary Angioedema that was treated in the hospital?		
A. Yes	95%	75%
B. No	5%	25%
10) If you answered "Yes" to the previous question, how many times over the past year have you been treated in the hospital?		
A. One time	38%	0%
B. Two to five times	23%	100%
C. More than five times	38%	0%
11) When you have an attack of Hereditary Angioedema, what limitations in the activities of daily life do you experience? Choose all that apply.		
A. I cannot go to work or school	37%	100%
B. I cannot participate in family and social activities	31%	85%
C. I cannot participate in sport activities	15%	57%
D. I am unable to care for myself (for example, eating and dressing)	13%	57%
E. I am unable to care for my children	13%	57%
F. I feel left out	4%	57%
12) Which of the following medication(s) do you currently take to prevent Hereditary Angioedema attacks?		
A. Danazol or a similar anabolic steroid-based medication	5%	12%
B. Cinryze (C1-Esterase Inhibitor, intravenous)	24%	12%
C. Haegarda (C1-Esterase Inhibitor, subcutaneous)	12%	25%
D. Other	39%	75%
E. Currently, I do not take any medications to prevent Hereditary Angioedema attacks	20%	0%

13) Which medications do you use or receive from your healthcare provider to treat acute attacks of Hereditary Angioedema? Choose all that apply.		
A. Berinert (C1-Esterase Inhibitor)	33%	18%
B. Ruconest (Recombinant C1-Esterase Inhibitor)	8%	45%
C. Firazyr (Icatibant)	43%	54%
D. Kalbitor (Ecallantide)	13%	18%
E. Other	3%	0%
14) If you or your caregiver administer(s) treatment for acute attacks, when is your treatment administered?		
A. No symptoms appear, but I can feel an attack coming on	33%	62%
B. Once symptoms interfere with my activity	8%	0%
C. Once pain or discomfort from swelling becomes intolerable	43%	25%
D. Only for throat or facial symptoms	13%	12%
E. I do not self-administer treatments: I seek medical care when I feel that treatment is needed for a developing attack	3%	0%
15) Aside from the cure, when considering a new treatment for your condition, which benefit(s) would you consider to be the most meaningful? Choose up to two.		
A. Reduction in attack frequency	36%	75%
B. Reduction in attack severity	23%	50%
C. Rapidity of response to treatment of acute attacks	25%	50%
D. Completeness of response to treatment of acute attacks	16%	25%

16) Of the following factors, which three would you rank as most important to your decisions about using treatments to treat your condition? Choose up to three.		
A. How the medication is administered (for example, subcutaneous, intravenous, etc.)	29%	100%
B. How frequently the medication is administered	16%	62%
C. Access to treatment (for example, cost, insurance coverage, or regional availability of the treatment)	27%	75%
D. Possibility of common and non-severe side effects (for example, headache, fatigue, short-lasting injection site pain	7%	12%
E. Possibility of infrequent but serious and severe side effects (for example, heart attack, stroke, blood clot in the lungs	12%	12%
F. Previous improvement in response to a similar treatment	5%	12%
G. Previous lack of improvement after another treatment	4%	0%
17) If you had the opportunity to participate in a clinical trial with investigational treatment for Hereditary Angioedema, which of the following best describes your thoughts about participating?		
A. Yes, I would consider participating	65%	62%
B. No, I would decline the offer to participate	5%	0%
C. Maybe, depending on various factors	30%	37%

18) What reason(s) would influence your decision for study participation? [Note: Please keep in mind that to participate in some trials you might need to temporarily discontinue your current prophylactic treatment or receive a placebo (inactive product) for a period of 3-6 months.] Choose all that apply.		
A. My current treatment does not work as well as I would like it to work	25%	62%
B. My current treatment causes side effects	15%	0%
C. I think my condition is well controlled and my discontinuation of the current treatment will not result in occurrence of new attacks, so I am willing to participate in a new trial	7%	0%
D. I think my condition is well controlled, but I am willing to participate in a new trial as long as I can receive proper treatment with an FDA-approved product for acute attacks that might occur	53%	100%
19) Would you be willing to participate in a clinical trial in which you receive a treatment that may result in a cure but that might carry a small risk of serious side effects, such as cancer?		
A. No	72%	12%
B. Yes	16%	25%
C. Maybe	13%	62%
20) Would you be willing to participate in a study in which the course, or the natural history, of your condition and its treatment are monitored and assessed over time, but in which you will not receive any specific new treatment as part of the study?		
A. Yes	100%	100%
B. No	0%	0%