FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC) MEETING

Virtual Meeting

Friday, November 17, 2023

9:00 a.m. to 4:30 p.m.

Meeting Roster

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Takyiah Stevenson, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

DR. STEVENSON: Good morning. Before we get started, due to unforeseen circumstances, Dr. Au notified us that he cannot participate in today's advisory committee meeting. Dr. Carvalho will be the acting chairperson for today's meeting. I will now turn it over to Dr. Carvalho.

Call to Order

DR. CARVALHO: Good morning, everyone, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contract is April Grant, and her e-mail is currently displayed.

My name is Dr. Paula Carvalho, and I'll be chairing this meeting, and I will now call the November 17, 2023 Pulmonary-Allergy Drugs Advisory Committee meeting to order. Dr. Takyiah Stevenson is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. STEVENSON: Good morning. My name is

Takyiah Stevenson, and I am the designated federal officer for this meeting. When I call your name, please turn on your camera, unmute, and introduce yourself by stating your name and affiliation for the record. We will first start with the standing committee members.

Dr. Bacharier?

DR. BACHARIER: Good morning. Dr. Leonard Bacharier, Vanderbilt University Medical Center.

DR. STEVENSON: Dr. D'Agostino.

DR. D'AGOSTINO: Good morning. Dr. D'Agostino, the consumer representative. I am a patient advocate with the Cystic Fibrosis Foundation and a medical writer with BOLDSCIENCE.

DR. STEVENSON: Dr. Evans?

DR. EVANS: Good morning. This is Scott Evans from MD Anderson Cancer Center in Houston.

DR. STEVENSON: Dr. Garibaldi?

DR. GARIBALDI: Hi. Good morning, everyone. I'm Brian Garibaldi from Johns Hopkins in Baltimore.

DR. STEVENSON: Dr. Hamblett?

DR. HAMBLETT: Good morning. Nicole Hamblett

from the University of Washington and Seattle Children's Hospital.

DR. STEVENSON: Dr. Kim?

DR. E. KIM: Good morning. Edwin Kim from the University of North Carolina School of Medicine.

DR. STEVENSON: Dr. Rank?

DR. RANK: Good morning. Matt Rank from Mayo Clinic in Arizona.

DR. STEVENSON: I will now introduce our non-voting industry representative.

Dr. Carlson?

DR. CARLSON: Hi. I'm Dawn Carlson, industry representative, Abbvie.

DR. STEVENSON: Thank you.

I will now move on to our temporary voting members.

Dr. Carvalho?

DR. CARVALHO: Hi. I'm Paula Carvalho, University of Washington.

DR. STEVENSON: Dr. Coon?

DR. COON: Good morning. I'm Cheryl Coon. I'm a clinical outcome assessment researcher and

psychometrician at Critical Path Institute.

DR. STEVENSON: Dr. Courey?

DR. COUREY: Good morning. Mark Courey. I am an otolaryngologist from Mount Sinai Health System.

DR. STEVENSON: Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I'm a biostatistician at NIAID, NIH.

DR. STEVENSON: Dr. Kelso?

DR. KELSO: Good morning. I'm John Kelso. I'm an allergist at Scripps Clinic in San Diego.

DR. STEVENSON: Ms. Schwartzott?

MS. SCHWARTZOTT: Hello. I'm Jennifer Schwartzott, and I'm your patient representative.

DR. STEVENSON: Thank you.

I will now continue to the FDA participants.

Dr. Seymour?

DR. SEYMOUR: Good morning. My name is Sally Seymour. I'm the director of the Division of Pulmonology, Allergy, and Critical Care in the Office of Immunology and Inflammation at the FDA.

DR. STEVENSON: Dr. Karimi-Shah?

DR. KARIMI-SHAH: Good morning. My name is Banu Karimi-Shah, and I'm the deputy director of the same division as Dr. Seymour.

DR. STEVENSON: Dr. Chin?

DR. CHIN: Good morning. My name is Stacy Chin. I'm a clinical team leader in the same division.

DR. STEVENSON: Dr. Bean?

DR. BEAN: Good morning. My name is Rachel Bean. I'm a medical officer in the same division.

DR. STEVENSON: Dr. Zhang?

DR. ZHANG: Good morning. My name is Weiya Zhang, supervisory mathematical statistician from the Division of Biometrics III, Office of Biostatistics, CDER, FDA.

DR. STEVENSON: Dr. Kim?

DR. Y. KIM: Good morning. My name is Yongman Kim. I'm a statistical team leader in the same division.

DR. STEVENSON: Dr. Mayo?

MS. MAYO: Good morning. I am Susan Mayo, a mathematical statistician in the same division.

DR. STEVENSON: Thank you. I will hand it back to the chairperson.

DR. CARVALHO: For the topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson, and we look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

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

conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Stevenson will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. STEVENSON: The Food and Drug Administration, FDA, is convening today's meeting of the Pulmonary-Allergy Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own, as well as those imputed to them, including those of their spouse or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting;

expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves a discussion of new drug application, NDA, 215010, for gefapixant oral tablets, submitted by Merck Sharp and Dohme Corp., for the proposed indication of treatment of adults with refractory or unexplained chronic cough.

This is a particular matters meeting during which specific matters related to Merck, Sharp and Dohme's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting numbers, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Dawn Carlson is participating as a non-voting industry

representative, acting on behalf of regulated industry. Dr. Carlson's role at this meeting is to represent industry in general and not any particular company. Dr. Carlson is employed by Abbvie.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you, and I will turn it back to the chairperson.

DR. CARVALHO: Thank you, Dr. Stevenson, and we will now proceed with the FDA opening remarks from Dr. Stacy Chin.

FDA Opening Remarks - Stacy Chin

DR. CHIN: Good morning, and welcome to the

FDA Pulmonary-Allergy Drugs Advisory Committee meeting. My name is Stacy Chin. I am a clinical team leader in the Division of Pulmonology, Allergy, and Critical Care within the Office of New Drugs. Thank you to members of the committee, the public, and the applicant for taking the time to discuss the new drug application for gefapixant, for the treatment of refractory or unexplained chronic cough.

Gefapixant is an oral P2X3 antagonist that is a new molecular entity. The proposed indication is for the treatment of adults with refractory or unexplained chronic cough at a dosage of 45 milligrams twice daily. This simplified diagram depicts the cough reflex arc. Although cough can be volitional under cognitive control, cough is typically a protective reflex initiated by various stimuli, such as mechanical or chemical, that activates sensory vagal nerve fibers in the airway mucosa, which convey the information to the brain stem. The brain then generates an efferent signal to motor nerves in the expiratory musculature to produce cough.

The underlying pathophysiology of refractory or unexplained chronic cough is still being investigated but is thought to be related to the heightened sensitivity of the cough reflex that is triggered by low levels of stimulation. P2X3 is one of many types of sensory receptors on the vagus nerve that respond to noxious stimuli; and thus, antagonism with a product such as gefapixant may potentially suppress cough.

Chronic cough is typically distinguished from acute and subacute cough by a duration lasting greater than 8 weeks. It is a common condition primarily affecting older adult females. The natural history isn't well characterized, but symptoms often persist for years, and some patients have relapsing remitting symptoms. While chronic cough is often associated with an underlying condition, the proposed indication is targeting patients who have cough that is refractory to treatment or cough that has no obvious cause. Both fall under the umbrella of "chronic cough," a term that FDA will use for simplicity.

Unfortunately, chronic cough has limited treatment options, none of which are approved. FDA recognizes that chronic cough is a condition that can have substantial impacts on quality of life, and that there's an unmet need for safe and effective therapies. Gefapixant is the first application to be reviewed by FDA for this indication. As such, there is no established precedent for study design or study endpoints, nor prior experience with interpreting efficacy results.

The sources of clinical data in the gefapixant program are shown here. The 52-week randomized, double-blind, placebo-controlled, pivotal trials, P030 and P027 shown in the red box, will be the focus of the presentations and discussion today. The trials evaluated approximately 2,000 adults with refractory or unexplained chronic cough and included three treatment arms, gefapixant 45 milligrams, 15 milligrams, and placebo, all administered twice daily. The primary endpoints were 24-hour cough frequency assessed by the VitaloJAK cough counting system at week 24 and P030 and week 12 and P027.

As will be discussed in later presentations, FDA considers the validated recount coughs to be the appropriate data for the primary efficacy analysis, and that is the data shown here. The primary endpoint results highlighted in the shaded blue rose and red boxes demonstrated a relative reduction in the geometric mean ratio of 24-hour cough frequency with gefapixant. While the point estimate is similar, only one of the two trials reaches statistical significance; however, a relative reduction in a geometric mean ratio is inherently difficult to understand, and the large placebo response resulted in a small treatment difference in coughs per hour.

This small treatment difference becomes more apparent when looking at the absolute cough frequency, which is more intuitive. Here, we note the high baseline variability in coughs per hour and, again, the large placebo response, and this translates to a small reduction in absolute cough frequency in the gefapixant group compared to placebo, with a difference in the change from

baseline of only 1 to 2 coughs per hour based on descriptive statistics.

For the multiplicity-controlled secondary endpoints, awake cough frequency results mirror those of the primary endpoint. The only patient-reported outcome endpoint in the hierarchy was a responder analysis of the Leicester Cough Questionnaire, or LCQ, total score in Trial P030. Although this result was statistically significant, there are concerns about the meaningfulness of the 1.3 point or more threshold and concerns about the LCQ instrument itself. With a large placebo response, the remaining endpoints failed to reach statistical significance.

The applicant captured additional PRO secondary endpoints that were not controlled for multiplicity. As such, these endpoints are considered exploratory in nature. Even though there appear to be small differences between treatment groups, there are limitations to the interpretability of these results. This topic will be discussed further in the presentations you'll hear later today.

Regarding safety, the main risk identified

with the proposed 45-milligram dose of gefapixant are disturbances in taste. This adverse reaction was common with a rapid onset. While generally mild and reversible, taste disturbances did impact tolerability in the trial, leading to early treatment discontinuation. This is a fact that must be considered for a chronically dosed drug.

In summary, the key findings observed in the pivotal trials were a wide variability in baseline cough and a high placebo response. This led to a small reduction in the primary endpoint of cough frequency relative to placebo with a statistically significant result in one of the two trials. There was a small effect on some PRO endpoints, and the safety profile is notable for frequent but reversible disturbances in taste.

Acknowledging that the pivotal trial results show small treatment differences in cough frequency reduction and PRO endpoints, the main issue for discussion by the committee today is whether these results are clinically meaningful. We are uncertain if patients will perceive such a small reduction in

coughs per hour, and the interpretation is further complicated by the lack of an established threshold for what is considered a meaningful reduction in cough to patients.

Looking to the other efficacy endpoints, it's unclear that the PROs provide compelling evidence that the small reduction in cough is meaningful. We note that the treatment differences are small; that the clinically meaningful improvements in score for each PRO have not been established; that there are concerns about the LCQ instrument and that this is the only PRO endpoint that this was statistically significant; and finally, that none of the other PRO endpoints were controlled for multiplicity in the statistical testing hierarchy, and are therefore exploratory. Finally, given the common and rapid occurrence of taste disturbances with gefapixant, we are concerned that this could be a potential source of unblinding, introducing additional uncertainty to the small treatment effect.

With those issues in mind, I'd like to review the statute and regulations that apply to FDA's

approval process. The regulations require there to be substantial evidence of a drug's effectiveness to support an approval, as shown here. We note that totality of evidence does not appear in regulations. Substantial evidence of effectiveness is generally interpreted as requiring two or more adequate and well-controlled clinical investigations, each convincing on its own to establish effectiveness, or in other words, independent substantiation. It is well established that the effects must be clinically meaningful and that statistical significance alone will not suffice. This is the standard expectation for chronic cough development programs.

One of the issues we will be asking the committee to consider and discuss later on this afternoon is the benefit-risk assessment for gefapixant. In this slide, we provide a diagram of how FDA approaches the benefit-risk framework. We acknowledge that at times there may be a tension between the FDA's benefit-risk assessment, which takes into account the intended patient population as a whole, versus the individual assessment that a

healthcare provider and a patient may make. In this framework, we consider the therapeutic context, such as the rarity and severity of the condition; the landscape of available therapies approved and off label; and the evidence submitted in a marketing application to assess the benefits and the risks.

In the benefit-risk assessment, we must first start with benefit. We consider the nature of the benefit, is it curative or disease altering, or is it symptomatic improvement. We must also consider the magnitude and the persuasiveness of the evidence supporting a benefit. Finally, and most importantly, we must ask ourselves if the benefit is clinically meaningful. If the answer is yes, we then turn to an assessment of the risks and uncertainties, factoring in the severity of the risks and what amount of risk and uncertainty are acceptable based on the therapeutic context.

Based on this, we determine if the demonstrated benefit outweighs the risks and any residual uncertainty about those benefits and risks. If this is the case, our assessment of benefit-risk

is favorable; however, if it's determined that there's not a clinically meaningful benefit, a product can only confer risks even if the risks are mild in severity, leading to an unfavorable benefit-risk assessment.

I will now conclude the opening remarks with a preview of the discussion points and voting question that we would like the committee to keep in mind as we hear the presentations this morning.

Discussion point 1, discuss the evidence of effectiveness for gefapixant for the treatment of refractory or unexplained chronic cough in adults. Specifically address the following: the small reduction in cough frequency compared to placebo and the clinical meaningfulness of the reduction in cough frequency; the observed results from PROs and whether these results provide compelling evidence to inform the clinical meaningfulness of the reduction in cough frequency; potential unblinding of patients due to taste disturbance and its impact on interpretation of cough frequency and PRO results.

Discussion point 2, discuss the overall

benefit-risk assessment of gefapixant for the treatment of adults with refractory or unexplained chronic cough, a symptomatic condition. And the final voting question, does the evidence demonstrate that gefapixant provides a clinically meaningful benefit to adult patients with refractory or unexplained chronic cough, given the small reduction in cough frequency and results from PROs? We ask that you provide a rationale for your vote. If you conclude that there is insufficient evidence of a clinically meaningful benefit, describe the evidence that could be collected to show a benefit that is clinically meaningful.

This concludes the FDA opening remarks. Thank you for your attention. I will now hand the meeting back over to the chair, Dr. Carvalho.

DR. CARVALHO: Thank you, Dr. Chin.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to

understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the meeting.

Likewise, the FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

And now, we will proceed with the Merck Sharp and Dohme, LLC's presentation.

Applicant Presentation - Lisa Bollinger

DR. BOLLINGER: Good morning, members of the Pulmonary-Allergy Drugs Advisory Committee and

members of the FDA. I'm Lisa Bollinger, vice president, Global Regulatory Affairs at Merck. I will be introducing Merck's presentation on our new molecular entity, gefapixant.

Gefapixant is P2X3 receptor antagonist developed by Merck for the treatment of refractory and unexplained chronic cough. For much of the presentation, we will refer to refractory chronic cough as RCC and unexplained chronic cough as UCC. RCC is defined as a chronic cough lasting for longer than 8 weeks that persists despite optimal treatment of any underlying conditions, and UCC is a cough that persists for longer than 8 weeks for which no underlying etiology has been identified despite a complete medical evaluation.

RCC and UCC are serious diseases. Chronic cough has a prevalence of approximately 5 percent in the U.S. adult population, and a subset of approximately 5 to 10 percent of those patients presenting for care have RCC/UCC. Most patients are women over the age of 50, and these patients suffer a high disease burden with impact on their physical,

social, and psychological well-being. Female patients may have the added burden of cough-induced stress urinary incontinence. There are no FDA-approved treatments.

I'd like to take a minute to walk you through the regulatory timeline leading up to today's meeting. In June of 2017, Merck had an end-of-phase 2 meeting to reach agreement with the FDA on our phase 3 development program. In March of 2018, two pivotal studies, Protocol 027 and 030, were initiated. These are the first large randomized-controlled studies ever conducted in RCC/UCC.

In July of 2020, Merck had a pre-NDA meeting, where we were informed that the development program appeared adequate to support a new drug application, or NDA, for gefapixant, and in December of 2020, Merck submitted that application for review. In January of 2022, Merck received a complete response letter, or CRL, from the FDA. The CRL was based on the FDA's assessment that the cough counting system required additional validation.

Merck addressed these concerns regarding the cough counting system and also performed additional analysis for the Leicester Cough Questionnaire or LCQ. You'll hear more about this in a following presentation. In the intervening period, gefapixant was approved in Japan, Switzerland, and Europe. Merck has resubmitted the application, and did that in June of 2023.

The VitaloJAK system consists of a digital sound recording device, a compression algorithm, and trained cough analysts. The recording device captures sound from two different microphones. One is a lapel microphone like the type you might see a TV reporter wearing, and the other is a contact microphone that is like the head of a stethoscope attached to the chest wall.

The compression algorithm can operate in one of two ways. First, it compresses by removing non-cough sounds using both microphones, also called dual channel, and the second way uses just the chest wall microphone, which is called single channel. You can see in the middle box on the right an

illustration showing portions of an audio file that could be removed or compressed, resulting in a shorter file for counting. The cough analysts use these compressed recordings to determine the 24-hour cough counts. Regardless of which compression method is used, the cough analysts use both of the files from both microphones to do this count.

The development program for gefapixant included 19 phase 1 studies, three phase 2 studies, and two pivotal phase 3 studies. Merck also completed two phase 3b studies shown here in pink. The results of this extensive clinical development program, that included over 3,000 patients, has demonstrated the clinically meaningful treatment effect greater than placebo and the safety of gefapixant.

This is the agenda for the rest of Merck's presentation today, and here are the subject matter experts that are available to answer your questions. And now, I'll hand it over to Dr. Dicpinigaitis.

Applicant Presentation - Peter Dicpinigaitis

DR. DICPINIGAITIS: Thank you very much.

My name is Peter Dicpinigaitis. I'm a professor of medicine at the Albert Einstein College of Medicine and a pulmonary critical care physician at Montefiore Medical Center in New York. I'm also the director of the Montefiore Cough Center, one of the few specialty cough centers in the United States. For over 25 years, I've been very active in both treating patients with chronic cough and in doing cough-related clinical research. Today, I'm pleased to discuss chronic cough as a distinct condition and to describe the unmet need of our patients with RCC/UCC. I'm a paid consultant of the sponsor, but I have no financial interest in the outcome of this meeting.

Cough is an important protective airway defense mechanism that's initiated by sensory nerve activation in the airway. Cough helps remove mucus from the airway and prevents foreign material from entering the lungs. Cough is also stimulated by inhaled chemical irritants. Importantly, cough can present as a key symptom of many acute and chronic conditions. Unfortunately, in some people, the cough

reflex itself becomes dysregulated, causing cough to be triggered by low-level or inoculus stimuli that should not normally induce cough.

Over the last decade, we've learned about the neurophysiology of cough. We know that there are two main types of sensory nerve fibers involved in the cough reflex, the A delta fibers and the C fibers. A delta fibers are responsive to mechanical stimulation of the airway surface, including by mucus or by inhaled foreign material. C fibers are responsive to chemical stimuli, including signaling molecules and inflammatory mediators within the airway, or by other irritant agents such as capsaicin, which we use to stimulate cough in our laboratory studies. C fibers can sense many types of chemical stimuli by a number of receptors, as shown here in the figure, including P2X3.

Within the airway, in situations of stress, inflammation, or injury, ATP is released from bronchial epithelial cells. Extracellular ATP can then bind to purinergic receptors known as P2X3 receptors. These P2X receptors are ion channels that

are found selectively on C fibers and not on the mechanically sensitive A delta fibers. When ATP binds to P2X receptors on airway C fibers, this generates an ATP cough signal.

Interestingly, P2X receptors are also found on the gustatory nerve endings in the taste buds on the tongue, where ATP serves as a signaling molecule of taste sensations. Gefapixant is a P2X3 antagonist that prevents ATP from opening the ion channels, thus inhibiting the cough impulse by the C fibers. By inhibiting the ATP cough signal, gefapixant reduces cough, leading to the benefit in the clinical studies conducted in patients with RCC/UCC, which you'll see later.

Chronic cough in adults is defined by the American College of Chest Physicians, or CHEST Cough Guidelines, and is a cough lasting greater than 8 weeks. Chronic cough of any cause has a prevalence of about 5 percent, as demonstrated in population-based studies in the United States. The RCC/UCC population is a subset of patients with chronic cough, representing approximately 5 to

10 percent of chronic cough patients. The CHEST guidelines also describe the negative impact these conditions have on quality of life and recognize the need for effective treatment options. The clinical approach to RCC/UCC has been provided in the guidelines.

When evaluating a patient with chronic cough, the physician's primary task is to identify and treat potential underlying reversible causes of chronic cough. The paradigm that we physicians have been following for decades is if you have a patient who's a non-smoker, who's not on medications that cause cough, mainly the ACE inhibitors, has no relevant signs on physical exam, and does not have evidence of active disease on chest X-ray, then it's likely that that patient's chronic cough is due to one or more of three underlying ideologies.

The first relates to eosinophilic airway inflammation, which includes asthma and non-asthmatic eosinophilic bronchitis. The second is upper airway cough syndrome, previously known as post-nasal drip syndrome, often related to nasal or sinus disease,

and the third is gastroesophageal reflux. Unfortunately, in some patients, the chronic cough persists despite a thorough evaluation and appropriate empiric treatment trials against the potential underlying causes. These patients are then classified as having refractory chronic cough, RCC, or classified as having unexplained chronic cough, UCC. The 2020 European Respiratory Society Guidelines also provide a recommended clinical approach to chronic cough, as well as a description of RCC and UCC.

Although RCC/UCC patients can be heterogeneous, in practice we see a rather uniform clinical presentation. The cough is invariably or either completely dry or minimally productive, and our patients tell us that their cough is caused by triggers that don't make other people cough; for example, chemical fumes such as household detergents or perfumes, or cigarette smoke.

These patients also cough due to triggers that can stress the airway but don't normally cause cough, such as laughing, or singing, or talking on

the telephone. Very often, patients describe a frequent or even continuous feeling of a tickle or a scratch in the throat, or a constant sensation of mucus in the throat causing an urge to cough sensation, as if a cough is always imminent. Patients describe these sensations as being particularly troublesome. The clinical phenotype in these patients raises the concept of dysregulation of the cough reflex.

Compared to other respiratory diseases that have been studied, patients with RCC/UCC, as enrolled in the phase 3 studies, had an extremely high burden of cough, with a median of about 500 coughs per day at baseline. Although cough can now be measured objectively with the cough counting system, it remains a research tool that is not used in clinical practice. And it's important to note that it's not just cough frequency, but cough severity that contributes to the burden in these patients. Cough severity incorporates not only cough frequency but also cough intensity, as well as disruptions of daily life. These three components all significantly

impact patients suffering from RCC/UCC. You'll hear more about how gefapixant affects these domains from the patient's perspective later in the presentation.

RCC/UCC patients are frustrated not only by their condition, but also by their often lengthy diagnostic journey. They feel like they're in the dark as to the cause of their cough. Despite evaluation often by multiple physicians, they're not getting the answers or relief that they so desperately seek. To share their experience, some patients have recorded video testimonials, as posted by the European Lung Foundation, a patient advocacy organization. I've seen in my patients what a tremendous burden chronic cough has on quality of life.

As you can imagine, the continuous cough is debilitating and stigmatizing, but also burdensome is how it affects the patient's relationship with their spouse, family, and co-workers. Here are some statements that my patients have shared with me. "My job is speaking to people on the phone all day long. It's been impacting my work very badly. My constant

coughing was so disruptive to my workplace, that they put me in a separate corner office furthest away from my co-workers. I appreciate the effort made by my employer, but I feel so isolated."

Another patient told me, "I've been a home health attendant for many years, but my constant coughing made my employer and my patients afraid of me, thinking that I have something infectious going on." And one woman confided, "I used to be an active member of my church and sang in the church choir. Now, I can't even attend services because I fear one of my terrible coughing attacks occurring."

Another woman shared with me, "I haven't slept in the same bedroom with my husband for many years now. He's very loving and supportive, but he needs to get up early for work every day, and he can't be woken up through the night by my coughing. I feel guilty that my cough has affected our relationship this way." And finally, "I was a very active person and enjoyed going to the gym several times a week, but now a bout of coughing can occur at any time and make me lose my urine, so the fear of

this happening has stopped me from going back to the gym."

Given these very real patient experiences, it's important that we capture and measure the impact of cough when we evaluate potential cough therapies. The Leicester Cough Questionnaire, or LCQ, is a validated instrument developed to measure the impact of chronic cough on quality of life. The LCQ measures three specific domains, which are physical, social, and psychological. Total scores use to measure overall impact of chronic cough, but patients report that the items in each of the individual domains are important as well.

Cough-induced stress urinary incontinence is another important consequence of chronic cough, and it affects almost exclusively women. Cough-induced incontinence has been reported in over 60 percent of women evaluated for chronic cough and is now being understood as a socially debilitating complication of chronic cough, potentially causing multiple episodes of incontinence daily. And clinical trial data suggest that episodes of cough-induced incontinence

may be reduced with successful treatment of RCC/UCC.

It's important to understand that 100 percent cough reduction is not the treatment goal. In fact, even a partial reduction in cough frequency or intensity can be meaningful to a patient, significantly improving their quality of life. For example, reducing frequency can make a patient just comfortable enough to go out in public to a restaurant, concert, or church, for example. Likewise, reducing duration and intensity of coughing bouts could disproportionately reduce or even eliminate episodes of stress urinary incontinence.

Because there are no approved therapies for RCC or UCC in the United States, physicians are limited to off-label medications that are often ineffective and/or have intolerable side effects. For example, opioids are used, but of course these aren't a satisfactory option for a chronic problem. Also, centrally acting neuromodulators like gabapentin are used in an attempt to reduce the sensitivity in the central nervous system as opposed to gefapixant, which acts peripherally in the airway.

But in my experience, these centrally acting agents are effective for only a small percentage of my patients, and often the dose of the drug that is necessary to achieve cough suppression causes unacceptable side effects, mainly sedation. What we desperately need are safe, effective drugs to treat our patients with RCC/UCC.

In conclusion, chronic cough, once it's diagnosed as RCC or UCC following the CHEST guidelines, is a condition in which the normal protective reflex of cough has become dysregulated, leading to a cough that is induced by otherwise innocuous triggers, serves no protective or beneficial effect, and becomes a bothersome disruptive condition. RCC and UCC have a tremendous impact on quality of life, not only for the patient, but for loved ones and coworkers.

Currently, we do not have any drugs approved for chronic cough, and certainly what physicians are using off label are inadequate, often not effective, and often not tolerated. The drug class of P2X3 antagonist, now represented by gefapixant, in my

opinion has great potential to provide a safe, effective, non-narcotic, non-sedating therapeutic option for RCC/UCC, which is very much needed by patients suffering from this very difficult condition.

Thank you for your attention. Dr. George Philip will now present the efficacy data.

Applicant Presentation - George Philip

DR. PHILIP: Thank you, Dr. Dicpinigaitis.

Good morning. My name is George Philip. I'm an executive director of medical affairs at Merck. It's my pleasure to provide an overview of the efficacy data collected in the phase 2 and phase 3 clinical studies.

The gefapixant development program included over 3,000 patients with RCC/UCC in phase 2 and phase 3. The first phase 2 study, Protocol 06, provided initial evidence of efficacy in a small crossover study. Protocol 010 explored gefapixant doses from 7.5 to 200 milligrams and provided data that informed the design of Protocol 012, the phase 2b dose-ranging study.

After phase 2, gefapixant progressed into the first ever global phase 3 program to investigate a novel agent in RCC and UCC. The program comprised two replicative phase 3 studies, P2X3 protocols 027 and 030, that included the same patient population and the same clinical endpoints. Two phase 3b studies, studying the effect of gefapixant in recent onset chronic cough and cough-induced urinary incontinence, have also been completed.

The phase 3 entry criteria defined RCC and UCC according to the CHEST guidelines. RCC is cough for more than 8 weeks in the presence of underlying conditions such as asthma, upper airway cough syndrome, or GERD, and this cough persists despite guideline recommended treatments for these conditions. In these protocols, patients needed to be on stable treatment for underlying conditions for at least 2 months. Most were on therapy much longer than 2 months at study entry, and all patients continued this therapy for the duration of the study. UCC was defined as chronic cough in which no comorbid conditions were identified despite full evaluation,

according to CHEST guidelines.

A minimum one-year duration of chronic cough was selected for our pivotal trials to ensure time for full and appropriate evaluation of potential causes of cough, and thus to allow a high degree of confidence in the diagnosis of RCC/UCC. To ensure patients had sufficient level of disease to require treatment, a minimum score was required on a patient-rated Cough Severity Visual Analog Scale, VAS. The minimum was 40 millimeters out of 100, a threshold that was recently independently validated as indicating at least moderate severity of chronic cough. Other entry criteria were no smoking, no recent ACE inhibitors, no abnormal chest imaging after the onset of the cough, and no obstruction on spirometry.

In the phase 3 trial designs, both had three arms: 45 milligrams, 15 milligrams, and placebo. In Protocol 027, objective cough frequency data were collected over the initial 12 weeks, referred to as the main period because cough frequency was the primary endpoint. Over the

additional 40 weeks of blinded therapy, we continued to collect patient-reported outcomes, PROs, as well as safety through the 52-week duration. In Protocol 030, the main period for cough frequency was 24 weeks. During the 28-week blinded extension, PROs were measured, and safety, for the full trial duration.

Here are the key endpoints in the two trials. Coughs were counted over an entire 24-hour period as the primary endpoint, and just when the patient was awake during those 24 hours, awake cough frequency. Protocol 030 also included a fully powered analysis of responses on the Leicester Cough Questionnaire, LCQ, which measures the impact of cough on patients' lives as described by Dr. Dicpinigaitis. A clinical responder analysis specified the proportion of patients who had an increase from baseline of 1.3 points in the LCQ total score, a threshold validated as clinically meaningful by the developer of the LCQ.

As shown, Protocol 030 has a larger sample size than 027 because it was designed with sufficient

statistical power to test this LCQ endpoint, whereas Protocol 027 was powered on the primary endpoint. Finally, both studies assessed the proportion of patients with at least a 30 percent reduction from baseline in 24-hour cough frequency. This threshold is clinically meaningful based on published analyses of the phase 2b dose-ranging data.

For treatment and study status at the end of 52 weeks, the top row in green shows that most patients in each arm completed the full treatment. Discontinuations from treatment most commonly were due to an adverse event, AE, or withdrawal by subject. There was a higher rate of discontinuation due to an AE in the 45-milligram arm, while withdrawal by subject was similar across the three arms. The AEs leading to discontinuation from treatment in the 45-milligram arm were almost entirely non-serious events and often were taste-related AEs. About 60 percent of these discons [ph] in the 45-milligram group were specifically for taste-related AE, meaning about 40 percent of these were due to various other AEs not

related to taste. Discontinuations will be discussed further in the safety presentation.

Here, the phase 3 population characteristics match the published literature. In the pivotal trials, three-quarters of patients were women, similar to the female predominance seen in specialized cough clinics as published globally and specifically in the U.S. In this literature, age is in the 50s or 60s, as we also see here in the pivotal trials. A bit more than half of the patients were recruited from Europe, a bit less than a quarter of patients from North America.

Let's turn now to the baseline data for cough in the pivotal trials. At study entry, these patients were coughing on average for over 11 years without effective therapy. The average baseline 24-hour cough frequency was close to 20 coughs per hour, which translates to around 500 coughs daily for years. Awake cough frequency is a bit higher because in RCC/UCC, patients generally cough more while awake.

Cough severity was rated by the patient on a

visual analog scale. You will remember that at least 40 millimeters was required to enter the study. What we found was close to 70 millimeters on average at baseline. The average total score on the LCQ measure of cough-specific quality of life was around 10. Since the LCQ total score has a scale from 3 to 21, where a lower score shows lower quality of life, an average of 10 reflects burdensome cough.

Here are the primary analyses of each trial using the original data set as submitted to FDA at the end of 2020 and shown here as published in the Lancet. In Protocol 027, gefapixant 45 milligrams BID demonstrated an 18.5 percent reduction in 24-hour cough frequency relative to placebo at week 12. In Protocol 030, gefapixant 45 milligrams demonstrated a 14.6 percent reduction relative to placebo at week 24. Fifteen milligrams did not differentiate from placebo and will not be discussed further in this presentation.

What is also evident in these results is a large placebo response, 53 percent relative to baseline in protocol 027 and 57 percent in

Protocol 030. Still, in each trial, the reduction in cough by gefapixant statistically exceeded the placebo response, showing 62 percent reduction relative to baseline in Protocol 027 and 63 percent reduction in Protocol 030. The analysis of the primary endpoint in prespecified subgroups pooled across the pivotal trials shows cough reductions for gefapixant relative to placebo for each group. They're generally consistent with the results shown in all patients.

The cough counting system for these trials has three steps: recording of cough sounds for 24 hours; compression of these recordings to remove time periods without cough sounds; and counting of the coughs by a trained analyst. In the original data set for the original submission to FDA, the cough compression methodology, that middle step, was refined by the vendor during phase 3. After the CRL, a new validation study assessed a single method of compression that was applied to the recordings in the pivotal trials to generate the recount data set, and the study analyses were redone using the recounted

data.

The primary analysis methodology as specified in the protocols was the longitudinal ANCOVA, also called mixed model for repeated measures, MMRM. This approach excludes patients without baseline data or post-baseline data. In their review of the original submission, the European Medicines Agency requested us to apply a specific missing data method, multiple imputation followed by ANCOVA or MI-ANCOVA, which imputes missing data to allow the entire efficacy population to contribute to efficacy analyses. In the end, there were two data sets analyzed by two methods, based on regulatory requests to us. As you'll see in the next few slides, the analyses were highly consistent. Note these variations across analyses only apply to the cough frequency data. The patient-reported outcome data did not change after the CRL.

To compare the cough frequencies in the original and recount data sets, we start with the original data set shown here, then we overlay the results from the recount data set. As you see, the

recount results are remarkably similar to the original for the placebo and gefapixant treatment groups. Because the recount and original data sets were very similar, the analysis results were also very similar.

Here, we'll summarize the analyses done prior to the original regulatory submissions and those done after the submissions in response to regulatory requests. We begin with the original data set and the prespecified analysis method, the L-ANCOVA. These are the same treatment effects that were shown on the earlier line plot you saw as percent reduction relative to placebo at the primary time point for each study.

Next, we add the primary analysis method applied to the recount data set in light green, then for completeness, we add the MI-ANCOVA method applied to both datasets. We see that across the analyses provided in the original submission of gefapixant and those provided to agencies after the original submission, the results show consistency of the treatment effect.

Here we have the phase 2b and 3 studies side by side with Protocol 012, the phase 2b dose-ranging study on the left next to Protocols 027 and 030. For Protocol 012, shown are placebo and the 50-milligram dose, similar to the 45-milligram dose in Protocols 027 and 030. What is relevant here, the treatment effect of gefapixant, the reduction from baseline, is quite stable across each of these studies. What is different between the studies is the size of the placebo response.

Of course, the phase 3 studies are much larger, and these are the first phase 3 studies ever performed in RCC/UCC, as well as the largest ever randomized placebo-controlled trials in cough. Without previous phase 3 experience in RCC/UCC, what placebo response to expect in this setting is open to conjecture. It is consistent with the role of the central nervous system to modulate the cough reflex in RCC/UCC. It could also include components of expectations going into these first ever phase 3 trials and the impact of regression to the mean.

In their briefing document, FDA pointed to a

potential relationship between taste AE reporting and efficacy measures, asking if this impacts the efficacy of gefapixant. This is important to evaluate, and Merck has looked carefully at the trial data. What we observe is that the data actually do not support that efficacy is driven by the taste AEs. In the phase 2 dose escalation trial, Protocol 010, we explored doses from 7.5 to 200 milligrams. From a dose of 50 milligrams up to 200 milligrams, these doses showed essentially the same efficacy on cough frequency, but over these same doses, taste AE incidence increased markedly from just over 40 percent to almost 90 percent incidence of taste AEs at 200 milligrams; so marked increases in taste AEs through doses from 50 to 200 milligrams did not drive an increase in efficacy.

Remember also that while efficacy is a pharmacologic effect of gefapixant, taste AEs are also a pharmacologic effect, so a relationship between these two effects can be expected in patients on gefapixant, and it could be hard to separate these confounded effects in these patients. To assess the

question without such confounding, we have to look in the placebo group, noting that placebo patients did report taste AEs. In the pivotal trials, the data in the placebo group have no confounding pharmacologic effects. The placebo group data on the primary endpoint show that patients with taste AEs did not experience more cough reduction than patients without taste AEs. If there were an impact of experiencing a taste AE on efficacy, we would expect to see greater improvement in the placebo patients with versus without a taste AE, and this was not observed.

Having discussed our objective cough frequency data, I'll hand it over to Allison Martin Nguyen to speak about patient-reported outcomes.

Applicant Presentation - Allison Martin Nguyen

MS. NGUYEN: Thank you, Dr. Philip.

Good morning. My name is Allison Martin Nguyen, and I'm an executive director in the Patient-Centered Endpoints and Strategy group at Merck. For the phase 3 gefapixant program, we developed a comprehensive, patient-focused endpoint strategy. That strategy was based on the extensive

literature describing the unmet need in chronic cough, input from both clinicians and patients, and analyses of our phase 2 data to identify the most relevant concepts to measure.

Shown on the left are the concepts we identified to be most important from the patient's perspective and to inform regulatory decision making. These include reducing both cough frequency and the patient-relevant endpoints of cough severity, impact, and overall change. On the right are the measures used to capture each of those concepts.

The primary endpoint in phase 3 is based on objective cough frequency captured using the VitaloJAK system. To support the primary endpoint, we included four patient-reported outcome questionnaires. The Leicester Lester Cough Questionnaire was used to assess the impact of cough on patients' lives; the Cough Severity Diary and the Cough Severity Visual Analog Scale were included to assess cough severity; and the Patient Global Impression of Change was included to capture the patient's overall assessment of change in their cough

since the start of treatment.

The LCQ is a 19-item cough-specific measure developed to assess the impact of cough on the physical, psychological, and social aspects of patients' lives. Psychometric validation has shown the LCQ total score to be reliable and responsive to change and cough over time. The total score ranges from 3 to 21 and is the sum of the three domains, with higher scores indicating less impact of cough on patients' lives, and here are three sample items, one from each domain. Note that each item refers to the patient's cough or coughing, has a 7-point response option scale, and a 2-week recall.

The agency raised three main concerns with the LCQ questionnaire. The first concern, that of content validity, focused on evidence that the LCQ items were based on input from patients with RCC and UCC. The original item generation phase and item reduction phase of the LCQ were based on direct patient input in alignment with the FDA guidance. Following several discussions with the agency, we conducted a new qualitative research study which

confirmed the content validity of all three domains of the LCQ to patients with RCC and UCC.

FDA's second concern is related to the use of the total score to reflect the impact of cough improvement on patients' lives. The agency considers the psychological and social domains to be influenced by factors other than the treatment; therefore, they consider the physical domain more relevant. From what we heard from Dr. Dicpinigaitis from the extensive literature describing the debilitating impact of cough on patients, and from our own qualitative research, it is clear that the psychological and social impacts of cough are as, if not more, important than the physical impacts to patients. Importantly, in both phase 2, where we validated the LCQ for use in the RCC and UCC population, and in phase 3, the LCQ total score in all three domains are correlated with and responsive to improvements in cough frequency and support the primary endpoint.

Finally, to address the FDA's third concern, I will review the methods we use to estimate the

clinically meaningful or responder thresholds for the LCQ total score. Because patients and physicians may be unfamiliar with how to interpret scores from questionnaires like the LCQ, we use a responder analysis because it provides an intuitive result that is easily understood.

Consistent with the FDA guidance, we conducted a number of analyses using phase 2 trial data, which resulted in multiple thresholds that were discussed with the agency. For the LCQ total score endpoint, the thresholds we used were based on, first and foremost, the threshold published by the developer, which was estimated by anchoring mean changes in the LCQ total score against patient ratings of change. This threshold has subsequently been used in numerous studies to assess chronic cough.

Second, using our phase 2 trial data, we conducted both distribution and anchor-based analyses, which pointed to LCQ total score changes ranging from 1.3 to 2.3 as meaningful and predictive of ratings of at least minimally improved on the

PGIC. Those analyses have been peer reviewed and published, resulting in established thresholds.

Finally, after further discussion with the agency, we conducted additional anchor-based analyses of our phase 2 data to identify the degree of change in the LCQ total score, corresponding to patient ratings of much improved and very much improved. The results of those analyses, which were shared and discussed with the agency, pointed to the two higher thresholds of 3.3 and 4.1. It should be noted that a change of 1.3 on the LCQ total score, which has a range of 18 points, is consistent with the threshold accepted by the FDA for another patient-reported outcome used in the respiratory field, the St. George's Respiratory Questionnaire, in which 4 points on a 100-point total score is considered meaningful. As you will hear, the results across the 1.3, 3.3, and 4.1 thresholds consistently favored gefapixant.

Finally, shown is the PGIC, which is an important measure for clinicians because it provides a quick and easily interpretable metric to assess

patients over time. For those purposes, a global rating such as the PGIC should be correlated with a patient's underlying disease. Because objective cough frequency assesses only one dimension of cough, that of frequency, the correlation between the PGIC and cough frequency is expected to be low to moderate.

Shown are the correlations observed using the phase 2 data. As you can see, there is a moderately strong correlation between the PGIC and the percent change in 24-hour cough frequency versus a weaker correlation between PGIC and absolute change in cough frequency. This result is not unexpected. For example, a reduction of 5 coughs per hour will be more impactful to a patient whose baseline is 10 coughs per hour versus a patient whose baseline is 50 coughs per hour.

For the PROs included in the phase 3 studies, again we see sufficiently strong correlations that provide reassurance that the PGIC is an appropriate anchor for defining meaningful changes and is also, in and of itself, a measure useful for interpreting

meaningful changes in cough frequency from the patient's perspective. I will now present the PRO results from the phase 3 studies.

Presented here are the results of the LCQ responder analysis from the Protocol 030, which was powered for this key secondary endpoint. As shown, a greater proportion of patients treated with gefapixant were LCQ responders compared to placebo. The statistical metric used to compare these proportions is the odds ratio, which is statistically significant at 1.41, meaning patients treated with gefapixant were 41 percent more likely to be a responder than those who received placebo.

Shown on this forest plot are the pooled data for the three LCQ total score thresholds used to define a clinically meaningful response. These results demonstrate the superiority of gefapixant over placebo across each threshold and at each time point.

Shown here are the results of responder analyses for the Cough Severity Visual Analog Scale and the Cough Severity Diary displayed alongside the

LCQ results at the three time points. While these were not part of the multiplicity control, these supportive PRO analyses provide consistent evidence of the benefit of gefapixant over placebo.

This graph shows the LCQ total score for the gefapixant group versus placebo over 52 weeks. Notably, a greater increase in the LCQ total score was evident by week 4 of treatment, which was maintained over 52 weeks, indicating sustained benefit of gefapixant 45 milligrams over placebo. Similarly, shown here are the three domains of the LCQ, the physical, social, and psychological, which also demonstrate consistent benefit of gefapixant versus placebo over 52 weeks, as observed with the LCQ total score.

Shown here are the longitudinal scores for the Cough Severity Visual Analog Scale and the Cough Severity Diary. Both PROs demonstrate a durable benefit of gefapixant over placebo through 52 weeks. And finally, shown here are the PGIC results for Protocol 027 and the Protocol 030 at weeks 12 and 24. The bars represent the proportion of patients in each

group, reporting themselves in the top two best categories of the PGIC, much improved or very much improved. The percentages and 95 percent confidence intervals above the bars show the consistent benefit of gefapixant versus placebo on this patient rating of meaningful improvement in their cough.

Across the PROs, we looked first at the LCQ, a tool that's been validated for use in RCC and UCC. In Protocol 030, which was powered for this endpoint, gefapixant demonstrated statistically significant and clinically meaningful benefit. Across the LCQ total and domain scores, there were meaningful improvements versus placebo, including on each of the three thresholds for the total score.

For the Cough Severity Visual Analog Scale and the Cough Severity Diary, the likelihood of achieving a clinically meaningful response was higher for gefapixant versus placebo at each time point and for each endpoint. For the Patient Global Impression of Change, a greater proportion of patients treated with gefapixant reported their cough as much or very much improved versus placebo. These data clearly

demonstrate that the efficacy observed is clinically meaningful to the patients treated with gefapixant, and now, I'll hand it back to Dr. Philip. Thank you.

Applicant Presentation - George Philip

DR. PHILIP: Thank you. Let's turn now to the phase 3b randomized, placebo-controlled studies because they support the benefits of gefapixant, including the clinical meaningfulness of the treatment effect. Both protocols were 2-arm studies of gefapixant 45 milligrams BID versus placebo, with the primary endpoint analyzed at the end of 12 weeks.

Protocol 043 is a study of recent onset chronic cough. This study enrolled patients who met the definition of RCC/UCC as in the pivotal trials but had a duration of chronic cough for less than one year. Protocol 042 is a study of women with RCC/UCC and urinary incontinence, in which the primary endpoint analyzed episodes of incontinence reported by the patient as triggered specifically by cough and not by other triggers of SUI.

Both trials met their primary endpoints, which were reported by the patient. Both provided

additional safety data with no new findings. The improvements in the cough PROs were very consistent with the improvements observed in the pivotal trials. In Protocol 042, this improvement in cough caused significant and clinically meaningful reductions in cough-induced SUI episodes.

In conclusion, gefapixant has demonstrated clinically meaningful and consistent efficacy in each of the seven efficacy studies in the program. In the pivotal trials, the treatment effect was consistent across the original and recount datasets. Reductions in 24-hour cough frequency, the primary endpoint, are clinically meaningful, as substantiated by asking each patient to rate how they felt on therapy compared with before therapy on PRO endpoints that are relevant to them.

First, on cough frequency, reductions more than 60 percent relative to baseline were shown. Percent reduction from baseline is meaningful to patients rather than a reduction of an absolute number of coughs, which patients don't have in mind. The PROs show clinically meaningful responses even

when defining the clinical responder using multiple thresholds, and the long-term durability as reported by the patients is consistent over 52 weeks. The phase 3b studies provide supportive efficacy, including in cough-induced incontinence as a complication of RCC/UCC at a level of placebo-adjusted efficacy on cough that is very similar across the phase 3 and phase 3b studies. All of these data provide substantial evidence of the effectiveness of gefapixant for treatment of RCC/UCC.

Thank you. And with that, I'll turn to the safety presentation by Dr. Willis.

Applicant Presentation - English Willis

DR. WILLIS: Thank you, Dr. Philip, and good morning. My name is English Willis, and I am the safety physician for the gefapixant program. Over the course of the development program, including both cough and non-cough trials, more than 3100 patients have received at least one dose of gefapixant. The 2,019 patients in the phase 3 trials include the 1,369 patients from the pivotal trials, Protocols 027 and 030, plus 650 patients from phase 3

country-specific and phase 3b studies. The safety findings from these studies were consistent with the safety findings from Protocols 027 and 030.

This presentation is focused on the safety data from the Protocols 027 and 030 pool, in which 633 patients were exposed to gefapixant for 52 weeks or more. Patients treated with gefapixant 45 milligrams BID experienced a higher incidence of adverse events overall and drug-related AEs as assessed by the investigator compared to those treated with gefapixant 15 milligrams BID or placebo. Serious AEs were infrequent and balanced across all treatment arms, and no deaths were drug related.

Discontinuations due to an AE and discontinuations specifically due to taste-related AEs were dose related. Based on the efficacy data and the sponsor's plan to file with only the 45-milligram dose, the remainder of my presentation will focus on gefapixant 45 milligrams and placebo doses from the 027 and 030 pool at 52 weeks. Of note, both studies were largely completed prior to the COVID-19 pandemic.

Within the gefapixant group, the five most frequently reported events were dysgeusia, often described as metallic, salty, or bitter taste; ageusia; hypogeusia; nausea; and taste disorder. Aside from the taste-related events, there were few AEs with an incidence of 5 percent or greater and where the incidence in the gefapixant group exceeded that in the placebo group.

While taste-related events were more frequent in the gefapixant group, these events were also reported by patients in the placebo group. Sixty-five percent of patients treated with gefapixant reported a taste-related AE, with the dysgeusia reported most frequently. Taste disorder represents events for which the patient was not specific in how they describe their changes or alterations in taste.

The incidence of serious adverse events were low and balanced across the the two treatment arms, and there were no serious taste-related AEs. The majority of patients with taste-related AEs remained on study treatment for 52 weeks. Taste-related AEs

experienced by patients treated with gefapixant resolved in most cases, occurred early in the course of treatment, were mostly mild or moderate in intensity, and had a median duration of 194 days. Taste-related AEs in 96 percent of patients on gefapixant resolved while on treatment or after the last dose. Resolution while on treatment occurred at a median of 65 days. For those in whom the event resolved after the last dose and by database lock, the median day of resolution was 5 days after the last dose.

We also evaluated whether taste-related AEs led to any clinical sequelae, and none were found. In comparing patients from the two arms with and without taste-related AEs, the overall frequency of potential clinical sequelae in patients with taste-related AEs was low, as were AEs suggestive of weight loss or dehydration. We also reviewed baseline weight, BUN, and creatinine, and compared those measurements to measurements obtained at the last dose, after discontinuation, or at the end of the study, and we found no meaningful changes.

Overall, adverse events leading to discontinuation were more frequent in the gefapixant group compared to placebo. The most frequently reported events leading to discontinuation were taste related, with discontinuations likely related to tolerability.

To summarize, gefapixant 45-milligrams BID in adults with RCC or UCC has an acceptable safety and tolerability profile. Comparable to placebo, there were few serious AEs and none were taste related. Taste-related AEs were the most frequently reported AEs, and these were mostly mild, not associated with clinical sequelae, and most patients tolerated the event and remained on study treatment, and taste-related events were reversible and resolved in 96 percent of the patients in the gefapixant group.

Thank you, and Dr. Jackie Smith will now share a clinical perspective on the benefit-risk profile for gefapixant.

Applicant Presentation - Jaclyn Smith

DR. SMITH: Thank you for the introduction, Dr. Willis. My name is Jackie Smith. I'm a pulmonologist and a professor of respiratory medicine

at the University of Manchester in the UK. I've been investigating chronic cough and its treatment for approximately 20 years now, and I've led many of the trials in the development of gefapixant that you've heard about today. I also set up and run a clinic caring for patients with chronic cough in Manchester. I'm a paid consultant to the sponsor, but I've got no financial interest in the outcome of this meeting, and today, I'm going to talk about the clinical perspectives on the benefit-risk relationship for gefapixant.

The diagnostic journey for patients with refractory and unexplained chronic cough is burdensome, as you can see from this slide. Each time the patient is evaluated, more tests are performed and treatment trials are administered, and these often get repeated. In my own clinic, chronic cough patients have typically been coughing for about 5 years at the point at which they're referred, and there are probably a couple of reasons for this.

First of all, refractory and unexplained chronic cough are generally under-recognized, and

therefore, physicians continue to search for an underlying cause. Secondly, there are just no licensed treatments to address this condition, so it's not unusual for patients to be coughing for more than 10 years. During this time, they suffer chest pain, broken ribs, low work productivity, social isolation, and overall poor quality of life compared to their healthy counterparts. Since the COVID pandemic, they're also stigmatized by their coughing.

With the lack of approved therapies, physicians result to off-label use of treatments such as opioids, neuromodulators, including gabapentin and pregabalin, and sometimes also other antitussives, including over-the-counter cough medicines. These treatments all have action in the central nervous system, and therefore, they tend to be accompanied by significant adverse effects. There's a lack of robust evidence for use of any of them, and the risks of side effects and potential for abuse of both opioids and gabapentinoids is not unsubstantial, and their implementation and use in clinical practice is really quite highly variable.

In contrast, gefapixant has a specific mode of action at P2X3 ion channels found on unsensory nerve fibers in the peripheral nervous system, and it has no action in the central nervous system. The efficacy demonstrated in the gefapixant trials is consistent with the notion that refractory and unexplained chronic cough is a specific disorder characterized by excessive activation of P2X3 by ATP, not just a failure on the part of physicians to identify and treat comorbid conditions.

Unfortunately, there are no therapies with robust efficacy for this condition. Even medications that are currently widely used to treat cough are unable to show effects of both that of placebo in clinical trials performed using modern methods such as objectively measuring cough frequency from audio recordings.

In the trial, you see here of a single dose of dextromethorphan for cough due to upper respiratory tract infection, there was an obvious reduction in objective cough frequency from baseline with active treatment; however, this treatment did

not differ from the large placebo response also observed in that trial. In my own study of codeine for coughing patients with stable COPD, both codeine and placebo showed statistically significant improvements from baseline and objective cough frequency, but when comparing the two treatment arms in this trial, codeine was unable to differentiate from the placebo. Notably, a 60 percent placebo response has also been observed in a similar population of refractory and unexplained chronic cough patients who were randomized to a study with the P2X3 receptor antagonist, sivopixant.

The reduction in cough from baseline is remarkably similar across the phase 2 and phase 3 studies as you see here, and it doubles the clinically meaningful change in cough frequency of a 30 percent reduction from baseline. What appears to change between the studies is the magnitude of the placebo response. Despite the placebo response, we're still observing a statistically significant benefit in the prespecified analysis, which confirms the true treatment effect of gefapixant. Of course,

phase 3 provides the larger more robust studies, and these are the first phase 3 studies ever performed in refractory and unexplained chronic cough, as well as the largest ever studies that we've performed in chronic cough.

Without previous phase 3 data, it was difficult to anticipate the magnitude of placebo effect that we might see, but it is consistent with what we know about placebo responses and cough and also in other therapeutic areas, and it's consistent with other data that have been published recently in phase 2 studies of refractory and unexplained chronic cough. Compared to placebo, the effect of gefapixant remains clinically meaningful, but the real benefit is the 60 percent change from baseline. This is what patients care about, and it's what they will experience; and as a physician, placebo isn't something that I can prescribe.

The effect of gefapixant in refractory and unexplained chronic cough was also replicated in patients with more recent onset chronic cough; that is, patients with a cough duration of less than a

year. In this study, the primary endpoint was cough-specific quality of life measured by the Leicester Cough Questionnaire rather than cough frequency, but as you can see from the graphs on this slide, the improvement in the LCQ for patients with recent onset chronic cough was very similar at 12 weeks to that observed in the pooled data from the phase 3 studies at 52 weeks. So if anything, these recent onset patients improved a little more rapidly.

Furthermore, gefapixant has also been demonstrated to impact on one of the common complications of refractory and unexplained chronic cough, stress urinary incontinence. On the left-hand graph, you can see here that gefapixant 45 milligrams reduced cough-induced incontinence episodes by 50 percent, and this was statistically significantly more than the reduction we saw with placebo. This was accompanied by a reduction in reported cough severity captured by the Cough Severity Diary, as you can see in the middle. On the far right, one can see that the Protocol 042 results are also consistent with what we observed on the Cough Severity Diary for

the entire pivotal phase 3 pool, which also shows continued improvement over 52 weeks.

So I've been involved in the development of gefapixant since I led the very first proof-of-concept study in my clinic in Manchester, which used the VitaloJAK cough monitoring system that I led the development of. Patients with refractory and unexplained chronic cough included in the phase 3 trials had an extremely high burden of cough compared to all the other respiratory diseases that I've studied, with a median of 500 coughs per day at baseline. But it's important to note that it's not just cough frequency that contributes to burden in these patients. Cough severity also incorporates intensity or the harshness of the coughing, as well as the disruption it causes to daily life.

Cough severity and cough stress urinary incontinence, for example, is very disruptive for patients. These data show that the benefit of gefapixant goes beyond simply reducing cough frequency. It has also consistently improved the burden of chronic coughing and an important

disruptive complication in women, stress urinary incontinence.

Also consistent throughout the studies to date has been the safety of gefapixant. While there have been no significant safety concerns, from the very first studies, we've noted taste-related disturbances, which is much more about tolerability. As the diagram suggests, I believe that patients will weigh the burden of their disease in terms of the frequency, intensity, and disruption of their coughing with the benefits that they gain from gefapixant therapy against the side effects that they might experience. This sort of balance is something that physicians caring for patients with refractory and unexplained chronic cough are already very familiar with.

As you're aware, the only treatment options that we have are unlicensed therapies that have shown some benefit in single small trials, and these include therapies such as low-dose morphine and gabapentin, both of which are associated with considerable side effects. So based upon my

long-term experience with gefapixant, I'm confident clinicians can appropriately manage patients' expectations and use shared physician/patient decision making to provide this therapy where it's most appropriate. Therefore, gefapixant has the potential to produce significant improvements in cough and the quality of life for patients with refractory and unexplained chronic cough.

Thank you, and I will now invite Dr. Bollinger to come to give some closing remarks from the sponsor.

Applicant Presentation - Lisa Bollinger

DR. BOLLINGER: Thank you, Dr. Smith.

You've heard from Drs. Dicpinigaitis and Smith that the reduction in cough counts and improvement in patient-reported outcomes observed in the gefapixant trials are clinically meaningful for patients. To help illustrate this further, I will use a framework from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, or IMMPACT, that appears in a publication by Dworkin, et al. This work was a collaboration between the

FDA, academia, and industry to address the challenges of placebo effect with pain trials that parallel those in cough. The clinical importance of group differences can only be established in the broader context of the disease being treated, currently available therapies, and the overall benefit-risk assessment.

On the left side of this framework are the factors that inform clinically meaningful efficacy at a group level. The first is the statistical significance of the primary efficacy endpoint. In the gefapixant trials, the results were statistically significant for the original count, and with the recount, the treatment effect was consistent with the original analyses. The magnitude of effect was the decrease in cough frequency of approximately 60 percent, consistently observed across both phase 2 and phase 3 studies.

There are no approved treatments for RCC/UCC and no established treatment effect for products used off label. We've conducted multiple responder analyses, and they all support the primary efficacy

endpoint. We have even looked at increasing thresholds in these analyses, and they consistently show a greater effect for gefapixant over placebo. The onset of cough reduction with gefapixant occurs at least as early as our first assessment at 4 weeks, with durability shown through 52 weeks, and the analysis of the patient-reported outcomes showed consistent improvement for patients and was statistically significant in Protocol 030, the trial powered for this key secondary endpoint. The safety of gefapixant is well characterized and tolerated by patients. The majority of patients stayed in the trials despite the taste-related adverse events.

Gefapixant is a first-in-class peripherally acting medication to treat RCC/UCC, offering patients a safe alternative to off-label treatments. Based on the totality of data and applying this framework, we conclude that the group differences are clinically meaningful. As you've heard in today's presentation, RCC/UCC has a unique pathophysiology with dysregulation of the cough reflex, and it can be debilitating for patients. There are no approved or

proven treatment options.

The totality of data across seven studies provides substantial evidence of effectiveness. Positive data across subjective cough frequency and patient-reported outcomes, including from studies of recent onset cough and cough-induced stress urinary incontinence, demonstrate that the treatment effect is not a chance finding and is meaningful for patients. As discussed, safety is well characterized with no imbalance of serious drug-related adverse events. The taste-related adverse events are mild and reversible and a tolerability consideration.

In conclusion, the consistent benefits of gefapixant far outweigh the risks and support approval for RCC/UCC. Thank you for your time and consideration, and we look forward to answering your questions.

DR. CARVALHO: Thank you very much to Merck for those presentations.

Now, we're going to take a quick 10-minute break, so panel members, please remember that there should be no discussion of the meeting topics with

other panel members during the break, and we'll resume at 10:45.

(Whereupon, at 10:32 a.m., a recess was taken, and meeting resumed at 10:45 a.m.)

DR. CARVALHO: Okay. Thank you.

We'll now proceed with the FDA's presentations, starting with Dr. Rachel Bean.

FDA Presentation - Rachel Bean

DR. BEAN: Thank you.

Good morning, everyone. My name is Rachel Bean. I'm a physician and a medical officer in the Division of Pulmonology, Allergy, and Critical Care in the Office of New Drugs. I will begin the FDA presentation, and you will also hear from my colleague, Susan Mayo.

Here's an outline of our planned presentation. I will begin with an overview of the clinical program, and then provide a focused safety review. This timeline lists the major regulatory events during clinical development of gefapixant for chronic cough, beginning with milestone meetings that occurred while the applicant was designing the

pivotal trials.

The NDA was submitted in 2020. FDA reviewed the NDA and issued a complete response in 2022, the reasons for which will be described in the following slides. Following the complete response action, additional meetings focused on resolution of the program's deficiencies were held, and the NDA was resubmitted in June 2023. Today's advisory committee meeting occurs during FDA's review of the NDA resubmission.

The initial NDA submission consisted of evidence from two pivotal trials, P030 and P027. This application received a complete response with the primary deficiency being insufficient validation of the cough counting system used to assess the primary endpoint of cough frequency. FDA could not verify that the endpoint results were accurate and reliable. Additional concerns with the program included the primary endpoint results, showing a small reduction in cough frequency of unclear clinical meaningfulness. In addition, the secondary endpoint results are not statistically persuasive and

are of unclear clinical meaningfulness.

This slide describes in blue boxes the key steps of the cough counting system used to produce the original unvalidated cough counts. The white boxes display the deficiencies in the system. In the first step, the VitaloJAK device is worn by each subject while it records potential cough sounds. It is important to note that the VitaloJAK device holds an FDA 510(k) clearance as an audio recording device only. This does not include compression or cough counting.

In step 2, the audio recording is compressed by an algorithm to remove silence and non-cough sounds. For compression, three non-equivalent algorithms which were not validated were used. The assignment of the specific algorithm to compress each sample did not follow a standardized process. These issues led to concern about reliability and reproducibility of the compressed recordings.

Moving to the third step, a human cough analyst reviews the compressed recording audio and waveforms and tags the coughs. Tags are counted to

produce the cough counts. There was no evidence of equivalence in tagging of compressed and uncompressed recordings. Finally, there was not evidence supporting that the human cough analysts have equivalent performance.

The boxes on the bottom row display the actions taken to resolve these deficiencies and produce cough counts sufficient for efficacy review. First, the applicant selected a single compression algorithm. This was validated comparing compressed and uncompressed cough counts across the relevant range of frequencies, then the single validated algorithm was used to compress all recordings, which were then tagged and counted to produce the recounted validated cough count data. The two additional algorithms used to produce the original cough counts were not validated.

Finally, an inter-rater reliability study demonstrated that the performance of the different human cough analysts was equivalent. The results of these studies support the accuracy and reliability of the system that produced the recounted cough counts

only. FDA will present efficacy results based on the validated recounted cough counts.

Now, I will provide a brief overview of the five clinical trials provided by the applicant with the NDA resubmission. I will discuss how each trial contributes to our evaluation of efficacy and safety for gefapixant. P030 and P027 are the two pivotal trials that were included in the initial NDA submission, and they continue to provide the efficacy and safety data that are the focus of FDA's review. These are 52-week randomized, double-blind and placebo-controlled trials in 2,044 adults with a diagnosis of chronic cough. Both trials evaluated twice daily dosing of gefapixant 45 milligrams, gefapixant 15 milligrams, and placebo. The primary endpoint of 24-hour cough frequency was analyzed at week 24 in P030 and at week 12 in P027.

In this red box, you can see the three supplementary clinical trials included in the NDA resubmission. FDA has determined that these trials have limited ability to inform the efficacy evaluation. These trials' results are not discussed

in our presentation and are described in the briefing document for reference. I will now proceed to discuss the endpoints evaluated in the pivotal trials. I will start with the primary endpoint of 24-hour cough frequency.

The gefapixant program is one of the first clinical development programs for the treatment of chronic cough, so there is limited experience with efficacy endpoint selection for this indication. Typically, efficacy endpoints to evaluate treatment for a symptomatic condition should measure change in the most impactful symptoms according to patients. Often these are assessed by patient-reported outcomes or PROs. In chronic cough, there is limited regulatory experience with PROs, so FDA agreed that 24-hour cough frequency was a reasonable and primary endpoint.

The rationale supporting this endpoint includes, first, that it is objectively measured by recording and counting coughs. Second, when the pivotal trials were designed, the available phase 2 data estimated a 30 percent relative reduction in

geometric mean ratio of cough frequency for gefapixant compared to placebo. This endpoint also presents challenges for interpretation. Frequency captures one aspect of cough, but other aspects are also important to patients such as severity and coughing bouts. Additionally, FDA and the applicant did not prospectively identify the types of within-patient change in cough frequency that could be considered clinically meaningful.

Having reviewed this background regarding the primary endpoint, I will now discuss the other endpoints investigated in the trials. Each trial has two secondary endpoints related to cough frequency, awake cough frequency and 30 percent or greater reduction from baseline in 24-hour cough frequency. The only multiplicity-controlled secondary endpoint based on a PRO is a responder analysis of change in total score on the Leicester Cough Questionnaire, or LCQ, using a threshold of 1.3 points. This endpoint was included in the hierarchy of P030 and not P027. There were additional secondary endpoints as shown here, responder analyses on CSD, or Cough Severity

Diary, and Cough Severity VAS or Visual Analog Scale. These endpoints were not controlled for multiplicity. As such, these endpoints are considered exploratory in nature.

Now, I will share some general thoughts about PROs as endpoints for chronic cough. PROs offer several advantages. They provide valuable direct evidence, reflecting patients experiences, and as such, FDA encourages the use of fit-for-purpose PROs to support regulatory decisions. Additionally, PROs can provide insight about different aspects of disease control beyond objective cough frequency such as severity, coughing bouts, and related symptoms. These results could help us understand the impact of a chronic cough therapy in patients' lives.

There are also limitations with PROs for chronic cough that must be considered when interpreting endpoint results. As previously noted, there is a lack of regulatory experience with these PROs. Interpreting a PRO is complex. There should be sufficient qualitative and quantitative validity evidence provided to FDA by the drug developer to

support interpretation. A given PRO should measure a disease-related concept that is important to patients. The PRO must be shown to provide an accurate and reliable measure of this concept, and the treatment effect on the PRO score should be meaningful and understandable to patients.

An important limitation of the PROs used in the gefapixant program is the lack of established thresholds for meaningful within-patient change. To understand what a change in PRO score means, the drug developer should provide evidence to inform score interpretation. This information is essential to determine if the observed change will be perceptible to patients.

Now, I will discuss the PROs in the gefapixant program in more detail. Given the lack of experience with PROs in chronic cough, it was reasonable for the applicant to evaluate various PROs. The responder analysis of the LCQ total score was the only multiplicity-controlled PRO endpoint. This was analyzed only in P030, as noted previously. Other secondary endpoints based on PROs that were

assessed include additional analyses of LCQ, such as higher response thresholds for the total score and domain-level endpoints, CSD, and cough severity VAS.

These were not multiplicity controlled, so they are considered exploratory. Many were post hoc. As such, they have limited ability to contribute substantial evidence towards efficacy evaluation in the gefapixant program; however, we are presenting results from the other PRO endpoints for completeness because this is the first application for chronic cough, and we are interested in the committee's input on the PROs in this program.

Now, to establish a common background before presenting the trials' results, I'll provide a brief review of these PRO instruments. First, we have the LCQ. This is a 19-item PRO instrument that assesses cough symptoms and impacts over a 2-week recall period. Three 3 domains -- social, physical and psychological -- contribute to the total score ranging from 3 to 21. Higher scores indicate better health status.

The items in each domain reflect concepts

covering cough-related symptoms and impacts. As described in our briefing document, FDA has concerns about the interpretation of some items contributing to the total score. As noted previously, a responder analysis of change of at least 1.3 points in the LCQ total score was the only multiplicity-controlled PRO endpoint in P030 only.

Here we have the CSD. This is a 7-item PRO instrument completed daily that assesses the frequency, intensity, and disruptiveness of cough. Each item is rated on a scale of 0 to 10, resulting in a mean total score of 0 to 10, with higher scores indicating greater severity. As noted previously, the CSD was used in exploratory analyses only.

Finally, we have the Cough Severity VAS. This is a single-item PRO instrument completed each evening. As shown here, the subject is asked to rate the severity of their cough today using a visual analog scale with no cough on the left and extremely severe cough on the right. The subject's response is translated to a number from zero to 100, though these numbers are not displayed on the scale, as you can

see. As noted previously, the Cough Severity VAS was used in exploratory analyses only.

Because safety is not a focus of this advisory committee meeting, I will now provide a brief overview of the safety results before we move to efficacy. The main risk with gefapixant administration is the frequent occurrence of taste disturbances, including change, loss, or decrease in taste. Although these events are neither serious nor severe, taste disturbances are frequent, occurring in 65 percent of the subjects receiving gefapixant 45 milligrams compared to 7 percent of subjects in the placebo arm.

This Kaplan-Meier curve shows the time to onset of taste disturbance adverse events for the gefapixant 45-milligram arm in red and the placebo arm in gray. The X-axis shows days since the start of treatment. As you can see, taste disturbance has a rapid onset, occurring within days. It generally lasts until discontinuation of therapy, at which point it resolved in at least 96 percent of subjects. These effects on taste impact the tolerability of

gefapixant, leading to discontinuation of treatment in 14 percent of subjects who received the 45-milligram dose.

In addition to posing tolerability issues, taste disturbances may introduce bias into the efficacy evaluation of gefapixant. Subjects and investigators are appropriately made aware of this common side effect upon enrollment or study initiation. Taste disturbances occur frequently, affecting 2 out of 3 subjects who received gefapixant 45 milligrams. Based on these observations, there is concern for inadvertent unblinding of subjects or investigators. In the setting of the small treatment effects on cough frequency and PRO endpoints, this potential bias increases the uncertainty around the evidence for efficacy.

Thank you for your attention. I will now call on my statistical colleague, Susan Mayo, to present the efficacy review.

FDA Presentation - Susan Mayo

MS. MAYO: Thank you, Dr. Bean.

I am Susan Mayo, a senior mathematical

statistician in the Division of Biometrics III, Office of Biostatistics. I serve as the primary statistical reviewer for this application. We now turn to the statistical review of efficacy.

While a common condition, chronic cough is a novel therapeutic indication that lacks regulatory precedent, particularly regarding endpoint selection, analysis methodology, and interpretation of efficacy results. The primary endpoint for these two pivotal trials was cough frequency measured for 24 hours using the unit of coughs per hour at week 24 for Study P030 and week 12 for Study P027.

The FDA analysis of cough frequency was based on recounted data for the reasons described in Dr. Bean's presentation. There were two multiplicity-controlled secondary endpoints based on cough frequency, awake cough frequency and proportion of patients who achieved at least a 30 percent reduction from baseline in 24-hour cough frequency. A third multiplicity-controlled secondary endpoint in Trial P030 was proportion of patients achieving at least a 1.3 point increase from baseline in the LCQ

total score. The other secondary endpoints not under multiplicity control are listed here.

Here is the testing hierarchy in the two pivotal trials. In P030, the primary and secondary endpoints were tested in gefapixant 45 milligrams versus placebo, followed by 15 milligrams. In Trial P027, the primary endpoint was tested in 45 milligrams and then 15 milligrams, followed by two secondary endpoints tested by high and low dose, respectively. To illustrate the differences in the hierarchies, the 15-milligram comparisons to placebo have a blue background.

Now, to the results. Here is the subject disposition at the landmark time points of week 24, or week 12 for the main study periods. In these trials, the highest rates for both treatment discontinuation and study discontinuation were in the gefapixant 45-milligram arms. A notable reason for study treatment discontinuation was adverse events. The rates were highest in the gefapixant 45-milligram arms, 20 and 16 percent, respectively, for P030 and P027, compared to 5 to 8 percent and 3 percent for

the other arms, respectively. There were no appreciable differences in demographics and baseline characteristics across treatment arms. The study population is consistent with the characteristics of a chronic cough population.

Now, on to the primary efficacy results. The FDA presentation will be focused on gefapixant 45 milligrams and placebo. The applicant employed a mixed model with repeated measures for change from baseline in log-transformed, 24-hour cough frequency. The geometric mean at baseline for P030 was similar for the two treatment arms. In P 027, the placebo baseline value was somewhat higher due to an outlier over 1,000 coughs per hour.

The geometric mean for the 45-milligram arms in both trials decreased from 19 at baseline to 7 coughs per hour at week 24 or 12. The placebo arm in P030 decreased from 20 to 9 coughs per hour, and in P027, from 24 to 11. The primary summary measure, relative reduction in geometric mean ratio between gefapixant 45 milligrams and placebo, was 14.6 percent in P030 and 17.0 percent in P027.

Significance was attained in Trial P030 but not in P027.

Note the high placebo response, which was not observed in the applicant's phase 2 trial. The ratio between geometric means at the landmark time point compared to baseline in placebo patients was 0.43 and 0.47 in P030 and P027, respectively. The placebo arms in both trials had a 53 to 57 percent reduction from baseline. Results for the 45-milligram arms were slightly better, with a 61 to 63 percent reduction.

To assess the robustness of the primary analysis results, several sensitivity analyses were conducted. This table shows the primary analysis on the original data in the first row, and for context, the results from the recounted data as described in this last slide on the next row. All remaining analyses in this table were performed on the recounted data. The percent relative reduction to placebo in these analyses was fairly similar. In the recounted data, it ranges from 13 to 15 percent in P030 and 15 to 17 percent in P027.

The applicant provided forest plots that use the primary analysis method to look at various demographic and baseline characteristic subgroups. There was no identifiable subgroup that demonstrated a stronger trend in gefapixant efficacy for cough frequency consistently for both pivotal trials when considered by gender; region; age group; cough duration; RCC versus UCC diagnosis; baseline cough frequency; or cough severity VAS.

Given the complicated statistical calculation of the primary endpoint, the interpretation of clinical meaning of these results is a challenge, therefore we conducted post hoc descriptive analyses of the absolute cough frequency, a more intuitive expression of the primary endpoint. In P030 and P027, the baseline median cough frequencies were 20 to 26 coughs per hour with an upper range of hundreds of coughs per hour. Looking at the change from baseline at landmark time points, the median values for gefapixant differ from placebo by only 1 to 2 coughs per hour.

Here is the box plot that corresponds to the

table in the previous slide. Blue denotes placebo, yellow denotes the 15-milligram arm, and red denotes the 45-milligram arm. The boxes contain the 25th to 75th percentile interquartile range, with a median marked with a horizontal line. The Y-axis was restricted to 250 coughs per hour in order to see this level of detail for the majority of data. Examination of the median and 25th and 75th percentiles revealed small differences between treatment groups in cough frequency at the landmark time points, as shown by the overlap of the interquartile boxes.

We conducted another descriptive analysis of the cough frequency based on responder thresholds. These figures show the proportion of subjects by varying thresholds for percent reduction from baseline for both trials. The prespecified thresholds of 30, 50, and 70 percent reductions from baseline in cough frequency are noted, with the faint reference lines on that X-axis to provide context for those thresholds within the continuum of response, from 0 to 100 percent, with the sample size and

percent of responders noted below in color-coded text. There is a large proportion of placebo responders that tracks with the gefapixant responders. In most instances, there is a numerical difference in the proportion of responders for a percent reduction in cough frequency between gefapixant 45 milligrams and placebo. The magnitude of those differences is quite small.

To explore whether gefapixant treatment resulted in a benefit that is meaningful to patients, FDA reviewed exploratory anchor-based analysis using PGIC as an anchor. The PGIC asks a patient to describe their cough now as compared to the start of treatment, with options from very much worse to very much improved, as shown in this image. A patient's response on PGIC could be used to help interpret if their response to treatment resulted in a perceived global improvement in their cough.

Anchor scales are used as external criteria to define patients who have experienced a meaningful improvement in their condition. A range of change scores in the endpoint can then be derived from the

group of patients who identified as having experienced meaningful improvement based on the anchor. FDA guidance recommends the use of multiple anchors to inform decisions about a plausible range of meaningful within-patient changes. In the gefapixant program, the PGIC is the only PRO measure administered in the pivotal trials that would be considered reasonable as an anchor to define meaningful change in cough frequency.

These figures plot PGIC response categories on the X-axis, with the most favorable values on the left, against change in 24-hour cough frequency for the three treatment arms in both trials. There is no clear trend indicating a relationship between the change in cough frequency and PGIC scores. Additionally, there is no treatment separation from the 45-milligram or 15-milligram arms compared to placebo for these improved categories.

To summarize findings from this exploratory anchor-based analysis, we noted that both trials showed a low correlation between change in cough frequency with PGIC score. This poor association of

cough frequency with PGIC indicates that the change in cough frequency occurs nearly independently from patient-reported improvement in chronic cough as captured by PGIC. In other words, patients who reported feeling better per the PGIC were not necessarily those patients who were coughing less. This did not inform meaningfulness of change in cough frequency from the patient's perspective.

Next, I will discuss the secondary efficacy endpoints under multiplicity control. The same mixed effects, repeated measures model for the primary endpoint was applied for the log-transformed awake cough frequency. Awake cough frequency results mirror 24-hour cough frequency in both trials. Point estimates for percent relative reduction in geometric mean ratio were 15 to 16 percent in awake coughs per hour. The p-value was significant for P030 but not for P027.

Displayed in the next table, you can see the applicant's selected LCQ total score threshold of greater than or equal to 1.3 points increase and a threshold of 30 percent reduction in cough frequency,

which are the remaining multiplicity-controlled endpoints. While they are reported here for completeness, it is important to note there was not sufficient evidence to support these thresholds.

For LCQ total score, the odds ratio of 1.4, 95 percent confidence interval being 1.0 to 2.0, for the proportion of subjects reaching the 1.3 point increase was significant. The difference in proportion of subjects reaching the threshold was 3.3 percent between the 45-milligram and placebo arms, which was small. This endpoint was not in the testing hierarchy for P027. There was a lack of statistical significance for the endpoint of 30 percent or greater reduction in cough frequency in both trials.

And last, I will discuss the other secondary endpoints not under multiplicity control. All these endpoints are PROs. Similar to the thresholds described in the last slide, upon review, FDA has identified limitations and uncertainties with a responder threshold cutoff selected for each of these PRO endpoints. Because of these concerns and the

lack of multiplicity control in testing for statistical significance, the following results should be interpreted within this context.

This forest plot presents the odds ratios of these endpoints for each trial. A key feature of the forest plot is the no difference line, which for an odds ratio is at 1. The first odds ratio of 1.4 is for the LCQ total score of greater than or equal to 1.3 points in Trial P030 and was previously discussed. The odds ratio for this endpoint in P027 was 1.3, with a confidence interval that includes 1. For the Cough Severity Diary, CSD, score at the thresholds of 1.3 and 2.7 points, the 95 percent confidence interval for these odds ratios was greater than no difference in P030 but not in P027. For the Cough Severity VAS score at the threshold of 30 millimeters, the 95 percent confidence interval for these odds ratios was greater than no difference in both trials.

Odds ratios can be challenging to interpret clinically. A prespecified supportive analysis for difference in proportion of responders reaching these

thresholds was also conducted. The no difference line on this forest plot is at zero. The treatment difference was small across the secondary endpoints, ranging from 3 to 9 percent. It is worthwhile to note that the applicant's analysis for odds ratio implicitly imputes missing data based on a statistical model, while the analysis for difference in responders explicitly imputes missing data as non-responders. This difference in how missing data was handled explains the dissimilarity in responder proportions and confidence intervals for these two prespecified analyses.

For the summary of efficacy findings, there was a high placebo response with little added effect from gefapixant across the endpoints. The statistical significance for these multiplicity-controlled endpoints were marginal in P030 and were not replicated in P027. The primary 24-hour cough frequency, which resulted in a 15 to 17 percent improvement relative to placebo was difficult to understand. We also assessed the absolute cough frequency using descriptive

statistics, and a small treatment difference was observed there, too, of 1 to 2 coughs per hour. Treatment effect on secondary endpoints were also modest.

There was no established threshold for meaningful within-patient change in the threshold specified for these trials for cough frequency or for PROs. The potential unblinding due to taste disturbance in 65 percent of patients who took gefapixant 45 milligrams, compared to 7 percent of patients who took placebo, may have introduced bias from possible knowledge of treatment. This potential for bias is of particular concern when treatment differences are so small. Clinical interpretation of these findings is required.

That ends the statistical review of efficacy. Now, back to Dr. Bean for her presentation of clinical considerations.

FDA Presentation - Rachel Bean

DR. BEAN: Hello again. I'm Rachel Bean, clinical reviewer. Now, I will discuss discuss the clinical considerations on the gefapixant program.

Today, we are asking for the committee's input on the clinical assessment of efficacy for gefapixant. Numerous considerations as highlighted here contribute to the unclear clinical meaningfulness of the results. Starting on the left, there is a large placebo response observed across endpoints. To the placebo response, gefapixant adds a small treatment effect, which has marginal statistical significance.

The frequent occurrence of taste disturbances has the potential to cause inadvertent unblinding, which could affect the PRO endpoints in particular. Additionally, there are not established thresholds for meaningful within-patient change in endpoints evaluating cough frequency and PROs. To explore the effects of gefapixant, FDA and the applicant conducted many analyses that are post hoc and not controlled for multiplicity. Typically, our regulatory practice is to employ a prespecified multiplicity-controlled hierarchy to minimize the observation of seemingly positive results that are actually due to chance. Only those endpoints that

are prespecified and multiplicity controlled are considered to contribute substantial evidence towards efficacy.

In our review of gefapixant, we reviewed the exploratory analyses to provide supportive context for the multiplicity-controlled analysis, and we have presented these results to support the scientific discourse by the committee today. In combination, these issues and uncertainties make it difficult to conclude that the treatment effect of gefapixant offers a clinically meaningful benefit to patients.

Now, I will provide some clinical perspective on the results. I will begin with the clinical discussion of the primary endpoint. Let's pause to consider this table.

The geometric mean values for cough frequency are shown in the second and third rows. Regardless of treatment arm, at baseline, subjects cough roughly 20 times per hour. After 12 to 24 weeks on trial, whether a subject is treated with gefapixant or placebo, this decreases to 7 to 10 coughs per hour. On the next line, the geometric mean ratio of

post-treatment to baseline coughs is displayed. Below that is the corresponding percent reduction from baseline. There is a large placebo response with over 50 percent reduction in the placebo and gefapixant arms. Gefapixant provides a small additional reduction of 6 to 8 percent beyond the placebo effect.

Moving down, we see the primary endpoint measure. Based on the p-values, the treatment difference from placebo reached statistical significance in P030 but not in P027. Despite this, note that the values for relative reduction at 14.6 and 17 percent differ by less than three percentage points; therefore, the treatment effect size is rather consistent in both trials.

Because it is challenging to understand what these calculations and results mean for chronic cough patients, next we looked at the raw or absolute values for cough frequency. As we saw in these box plots, after treatment, the median cough frequencies and the 25th and 75th percentile values overlap across treatment arms. Median cough frequencies at

baseline and post-treatment are shown in blue for placebo and red for gefapixant. In both trials at baseline, the median cough frequencies were 20 to 26 coughs per hour. After treatment, hourly coughs reduced to 11 or 12 for placebo and 8 or 9 for gefapixant.

The results for median change from baseline are shown here. Gefapixant yields a reduction beyond the high placebo response of approximately 1 to 2 coughs per hour. The clinical meaningfulness of this small change is not self-evident and the degree of cough frequency reduction that corresponds to meaningful within-patient change has not been established. To assist in interpreting these effects on cough frequency, we look to secondary and PRO endpoints.

A post hoc analysis to explore how decreased cough frequency affects the patient experience is shown here. Each patient's response to the question, compared to the start of treatment, how would you describe your cough now, is plotted against change from baseline and cough frequency. In the trials,

very few responses fell in the worst categories, as reflected by the wide confidence intervals and absence of data on the right half of these figures. Meanwhile, the red squares highlight subjects whose PGIC response indicated that they feel the same or better.

There is overlap of the changes in cough frequency across these response categories. This suggests that patients who feel better based on PGIC are not necessarily those patients who are coughing less frequently. Further, within each response category, there is overlap of the color-coded treatment arms, highlighting the absence of a difference between placebo in blue and gefapixant in red.

Now, I will review other findings that may help us assess the change in cough frequency. Here, you can see the multiplicity control hierarchy of secondary endpoints. From the regulatory perspective, only the secondary endpoints within this hierarchy have sufficient statistical rigor to contribute substantial evidence towards efficacy.

The results shown first for awake cough frequency resemble those for 24-hour cough frequency, so this endpoint offers little additional information to help understand the primary endpoint results.

The responder analysis of LCQ total score using a 1.3 point responder threshold is multiplicity controlled in P030 only. The odds ratio meets statistical significance; however, the applicant has not provided sufficient evidence that a 1.3 point change in score is meaningful to patients. As shown in the last two lines of the red box, roughly 60 percent of subjects met the threshold of 1.3 points whether they were treated with gefapixant or placebo. The treatment difference between arms was small at 3 percent. Thus, it is not clear that the change detected on this endpoint is meaningful.

Finally, the responder analysis of 30 percent reduction in cough frequency showed no treatment difference from placebo, and 56 to 58 percent of subjects met this threshold whether they were on gefapixant or placebo. To examine other thresholds for reduction besides 30 percent, as shown in this

statistical presentation, we looked along the continuum from 0 to 100 percent response, comparing the percent of subjects in each treatment arm who met a given threshold, and we saw little to no separation between treatment arms.

Although the secondary endpoints evaluating other PROs were not multiplicity controlled and were therefore considered exploratory, we assessed the data to further our understanding of the results, and we are presenting these results to further today's scientific discussion.

For each of the PROs, the applicant chose to conduct responder analyses at various thresholds; however, there is not evidence that these specific thresholds represent a change in score that is meaningful to patients. As we just saw, the only PRO analysis included in the multiplicity hierarchy was the LCQ total score responder analysis reported as an odds ratio. Because odds ratios are challenging to interpret, this figure shows the percent of responders and the difference between treatment arms for the various PROs at the applicant's selected

thresholds.

If we consider the results at face value, the differences between gefapixant and placebo are small, at less than 10 percent across these endpoints with most confidence intervals crossing zero. In the context of potential unblinding due to taste disturbances, which could be especially relevant for PROs, we question whether these small treatment effects can be considered meaningful.

I would like to take this opportunity to summarize the clinical efficacy findings. Across endpoints related to cough frequency or PROs, patients improved whether they were treated with gefapixant or placebo. There was a small reduction in the primary endpoint of cough frequency relative to the large placebo response. The relative reduction in geometric mean ratio achieved marginal statistical significance in only one of the two pivotal trials, though the point estimates of the treatment effect are similar. Because the primary endpoint summary measure is difficult to translate clinically, we assessed the median change in absolute

cough frequency and found that gefapixant yields a reduction of 1 to 2 coughs per hour beyond the effect of placebo.

We conducted exploratory analyses to examine these effects on cough frequency. We analyzed correlation between the change in cough frequency and the PGIC score, and we found that coughing less often did not correlate with feeling better since the start of treatment. We conducted analyses in search of a subgroup of patients with increased responsiveness to gefapixant whom providers could identify in clinic and target for therapy. No such group was identified on subgroup analyses based on demographics and baseline disease characteristics. Evaluation of thresholds for reduction in cough frequency higher than 30 percent did not suggest a substantial benefit. Given these results, it is unclear whether the detected effect of gefapixant beyond the large placebo response is meaningful or perceptible to patients.

This slide summarizes the contribution of PRO results to the understanding of efficacy. First, I

will discuss the LCQ specifically, as this was the only PRO instrument that was included in a multiplicity-controlled endpoint. FDA has concerns about the content validity of this instrument, as outlined in the briefing document. These make it challenging to interpret score changes. The applicant did not provide sufficient evidence to demonstrate that a total score increase of 1.3 points represents a change that is meaningful to patients; therefore, we question the meaningfulness of the observed change in the total score.

If we look at the raw change in total score, the treatment difference was small at less than one point. Especially in the setting of potential unblinding, these small changes in PRO scores are not obviously meaningful and there is a lack of evidence to assist in rigorous interpretation of these score changes.

The results of the other PRO endpoints offer little additional support for efficacy. None of these endpoints were controlled for multiplicity. Like cough frequency and LCQ, there is no evidence to

support the selected responder thresholds or to define meaningful within-patient change on these PRO scores. If considered at face value, the responder analyses and raw scores on each PRO showed a small treatment difference from placebo.

Now, I will offer some concluding thoughts. FDA recognizes the need for safe and effective therapies for chronic cough. This is a common chronic, symptomatic condition that can deeply impact patients' lives, and there are currently no approved therapies for chronic cough patients in the United States. To demonstrate that a drug is effective, the evidence provided by the drug developer must show that the drug offers clinically meaningful benefit. This benefit should be distinct from the effect of a placebo control, and it should be not only statistically detectable and significant, it should also be clinically meaningful.

Due to the many issues and uncertainties identified in the gefapixant program shown here and discussed in our presentation, we cannot readily conclude that the small treatment difference between

gefapixant and placebo is clinically meaningful. While one might claim that there is no harm in making a product with uncertain effects available for patients to try for themselves, this approach does not align with FDA's standard for approval. Further, it can in fact harm individual patients and our broader society in ways including negative side effects; missed or delayed diagnosis; missed opportunities to take a more effective therapy; drug-drug interactions; pill burden; and increased healthcare costs, among others.

We ask that the committee keep these considerations in mind as you deliberate and discuss this application today. With that, I thank you for your attention, and I look forward to hearing the committee's thoughts today. This concludes the FDA presentation.

Clarifying Questions

DR. CARVALHO: Thank you very much to the agency for your presentation, and now we'll take clarifying questions for the presenters from Merck Sharp and Dohme, LLC, and the FDA.

Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. And finally, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so that we can move on to the next panel member.

Dr. Kelso?

DR. KELSO: Yes. John Kelso. I have a question for our FDA statistician. We've heard several times that many of these analyses are less robust, or reliable, or interpretable because of the lack of multiplicity correction. Is that something that's fixable? In other words, is that just a matter of going back to the computer and, in fact, doing a multiplicity analysis or correction on those

parts of the data so that they would generate more robust or usable data?

DR. CHIN: Thank you for that question, Dr. Kelso. This is Stacy Chin, FDA. So just to summarize your question for the FDA statisticians, it's about the lack of multiplicity control for several of the secondary endpoints, and is there anything we could do about it at this point?

DR. KELSO: Correct.

MS. MAYO: This is Susan Mayo, the primary statistical reviewer. What multiplicity adjustment does is it preserves the type 1 error, so when we talk about a cutoff of 0.05 for statistical significance, that is in association with just one comparison. So if we do a number of different statistical tests on a number of different comparisons of different endpoints, then that inflates that type 1 error, and it's no longer at 5 percent, which there's been a higher rate of spurious -- or it could just be by chance.

One very common way of addressing that is with multiplicity adjustment, and what that means is

declaring before the trial is unblinded what the hierarchy -- which I showed in one of my slides -- is for which endpoints will be tested first, and then if those are significant, then go to the next, et cetera. This cannot be adjusted once the data has been unblinded because then the results are available, so the way to adjust it is to declare those in the multiplicity hierarchy prior to the study being unblinded.

DR. KELSO: Okay. Yes, I think that does answer the question. It's, unfortunately, not fixable after the fact.

MS. MAYO: That is correct.

DR. KELSO: Okay. Thank you.

DR. CARVALHO: Thank you, Dr. Kelso.

Next is Dr. Garibaldi.

DR. GARIBALDI: Hi. Good morning, everyone. My question is for Dr. Philip and the Merck team. We've heard a lot about the large placebo effect that's been seen in both trials. I was wondering, to address the issue of whether or not participants were essentially unblinded by the taste side effects, did

you take a look at the the folks who did not experience taste side effects versus those who did, to actually look at the impact of the drug on their symptoms and how that compared to placebo? That might be one way of at least trying to look at what the additional potential impact of the unblinding impact of the taste side effects might be.

DR. BOLLINGER: Yes. We understand your question, and we have done several analyses. To your point, it is very difficult to untangle this in the active arm because P2X3 receptor antagonist, which is the way our drug works, creates both the taste-related adverse events and a reduction in cough. We have done multiple analyses, and I'll ask Dr. Philip to walk through those analyses with you.

DR. GARIBALDI: Thank you.

DR. PHILIP: Thank you, Dr. Bollinger.

Indeed, we have reviewed the data, which I can summarize from two perspectives, but to come directly to your question and in follow up to what you heard from Dr. Bollinger, we understand that gefapixant has a pharmacologic effect of efficacy,

pharmacologic effect of taste AEs. In order to tease apart those effects, the best place to look is in the placebo group. So if we can call up the slide that shows the placebo group comparison with versus without a taste AE, I think that's the point of your question.

Slide up. So what we see in the slide is that patients with the taste-related AEs did not have more benefit to patients without. This shows that the within-group comparison of those patients with and without taste AEs in the placebo group, the reduction from baseline at 52 percent in the patients without taste AEs was larger, actually numerically, than the reduction in the patients with the taste AEs. So clearly, the hypothesis that somehow reporting a taste AE is driving efficacy is not evident when we look at the data in this comparison that does not have the confounding of the dual pharmacologic effects. Thank you.

DR. GARIBALDI: Thanks for showing that. I know you briefly showed that previously, but I just wanted to go back to it.

DR. CARVALHO: Thank you, Dr. Garibaldi.

Next is Dr. Bacharier.

DR. BACHARIER: Alright. Thank you. I'll put the question out. I suspect Ms. Nguyen from the Merck side will be the the best to respond. One of the the clear differences in interpretation of the data we've seen this morning surrounds the PRO about the Leicester questionnaire, and if I recall correctly, in the sponsor's presentation, it was identified as one that has been validated with clinically relevant and detectable changes already described and published, whereas the FDA's perspective was seemingly contrary to that, and it did not seem to favor that a minimally important or minimally clinically perceptible difference has been described, and therefore, the cutpoints that were used in the analyses are less clear and evidence based.

I'm really trying to wrap my head around which of those two perspectives is the most accurate to what we understand, because I think it's actually going to be a relatively pivotal point in the

decision-making process for the committee. So if Ms. Nguyen could add anything to that, and if the FDA folks want to provide some comment, I would really appreciate it to help clarify my thinking around this.

DR. BOLLINGER: Yes, and you are correct that the LCQ has been validated. I'll ask Allison Martin Nguyen to come to the microphone to provide you with additional information.

MS. NGUYEN: Thank you. Yes, there is clearly a difference here in in our presentations. In the LCQ questionnaire development work, that 1.3 point threshold, as I said, has been published by the developer, and we then subsequently conducted those analyses in our phase 2 program. I should note that when we conducted those analyses in our phase 2 program, that was pooling our treatment groups together, which is a common method for conducting anchor-based analyses. So the threshold that we identified using our phase 2 data was not essentially cherry-picking what would look best for gefapixant; it was using pooled analyses.

Perhaps the FDA's concern is that we did not get a chance to talk to them about those thresholds prior to finalizing our phase 3 protocol; however, we did have subsequent discussions with the agency, wherein we returned to our phase 2 data, conducted those analyses again looking at higher anchor-based thresholds of much improved and very much improved at their request, and that's where the 3.3 and the 4.1 thresholds were discovered or estimated, and then applied in our phase 3 program. The original analyses that I talked about have been published and are in the peer-reviewed journal, so we consider those to be an established threshold. Thank you.

DR. BOLLINGER: For additional information, I'd like to call Dr. Birring, one of the developers of the LCQ, to the podium.

DR. BIRRING: Thank you Dr. Bollinger. It's Surinder Birring, developer of the LCQ, pulmonologist and professor of respiratory medicine. The LCQ, validated to assess the impact of cough, is widely used in our field. It's been recommended by the CHEST guidelines for managing cough. The

1.3 threshold was developed using an anchor-based method and rated by patients as being meaningful. It's widely used in the field, in specialist clinics, and also in clinical trials. As you have heard, we've looked at higher thresholds for much improved or very much improved, and the results were all consistent, favoring gefapixant over placebo. Thank you.

DR. CARVALHO: Dr. Bacharier, does that answer your your questions?

DR. BACHARIER: That is definitely helpful from the Merck perspective. I would politely ask if there's a reaction from the FDA to that additional set of comments.

DR. CARVALHO: We have Dr. Karimi-Shah from the FDA.

DR. CHIN: Yes. This is Stacy Chin from the FDA. I agree with you, Dr. Bacharier. This seems to be a central point of this committee discussion, so I'm going to call on my colleagues from the Division of Clinical Outcome and Assessment group to begin the discussion about the 1.3 threshold for the LCQ.

DR. LI: This is Ji Li. I'm the primary reviewer from the Division of Clinical Outcome Assessment, FDA, so I will start, and my colleague, Dr. Illoh, will continue with our additional concerns.

From FDA's regulatory consideration, there should be sufficient qualitative and quantitative validity evidence to support the interpretation that the PROs can reflect the concepts of interest in the target context of use. We acknowledge the applicant's qualitative study supports some of the concepts captured in the LCQ are relevant to the patient experience; however, some of the concepts are distal. In other words, they are not cardinal to chronic cough, and thus more heterogeneous and not well defined.

Also, some distal concepts, for example, embarrassed or worried about cough, or cough interferes with the enjoyment of life, and feeling cough has annoyed family, friends, or partner, are downstream from chronic cough and may be influenced by many other factors outside of the treatment or

condition. Therefore, we conclude the LCQ total score is not fit for purpose.

DR. ILLOH: Hi, everyone. This is Onyekachukwu, team leader in the Division of Clinical Outcome Assessment, and I would add to what Dr. Li has said. First, before I talk about the 1.3 threshold and the concerns we have, we have to be careful with using the term "validated." From our experience, from the regulatory experience, the term "validated" doesn't necessarily meet the regulatory requirement for what is considered to be a fit-for-purpose instrument. From FDA's regulatory perspective, an instrument is fit for purpose when there is great conclusion from all of the validity evidence that the instrument helps support the derivation of a well-defined and reliable endpoint, and that's not what was seen with the LCQ total score, given the issues we have with the distal concept.

Setting aside the issue of the distal concept, yes, we did take a look at the 1.3 threshold proposed by Raj, et al. in the 2009 publication, and

there are several methodological limitations with how that 1.3 threshold was derived. First, when you derive a threshold, you anchor it to a global scale that is inherently meaningful. They use the scale called -- I think it's called the Global Rating of Change Questionnaire. Raj, et al. used the Global Rating of Change Questionnaire to anchor the change in the LCQ total score, and one thing we have about the scale is that it's a 15-point scale with the response option ranging from plus 7 to negative 7, and these response options are not clinically distinct and they are overlapping.

Another issue with using the global rating of change scale used in the publication is that it's not clear what is considered meaningful on that anchor scale. That's paramount to getting a good threshold. And then most importantly, the way the threshold was derived is that the change in the LCQ total score was anchored to a small change on the anchor scale, and how a small change was defined was that they combined categories representing improvement and worsening.

So what that means is that the small change

on the anchor scale was defined as somewhat better, a little better, a little worse, and somewhat worse. These are combined categories indicating improvement and worsening, and we typically would not recommend this approach. If you are deriving an improvement threshold, then you should focus on an improvement response category on that anchor skill. And more so, the threshold for meaningful worsening or meaningful improvement is not symmetrical, so that's a methodological limitation with how that was derived.

Like we said, if we're to look at the improvement categories that were used, based on our experience and across multiple indications, patients have never endorsed somewhat better as meaningful on an anchor scale. So these are the main issues we have with how that 1.3 threshold was derived.

DR. GARRARD: Hi. This is Dr. Lili Garrard, statistician from FDA. Since the applicant also brought up the potential use of higher threshold on the LCQ total score, I do want to offer a clarification that these additional responder analyses were proposed by the applicant and not

requested by the FDA. While FDA had agreed to review these additional responder analyses, as Dr. Li mentioned earlier, we do not consider the LCQ total score to be fit for purpose, and this point was clearly communicated to the applicant in communication during the current review cycle. Therefore, any additional responder analyses based on the LCQ total score are viewed as exploratory only. Thank you.

DR. CARVALHO: I'd like to move on to the next panel member, but first I'd like to see if Dr. Karimi-Shah has a comment to make from the FDA, and also if the sponsor has a member here that I would like to get to as well.

DR. CHIN: This is Stacy Chin, FDA. Our team would just like to provide our perspective on the high placebo response and the impact that taste may have had on the response. I'll hand this over to the statistical review team.

MS. MAYO: This is Susan Mayo, primary statistical reviewer. Could I have backup slide 126, please? Here, we explored results of taste

disturbance on cough frequency. One thing we've discussed internally is we're not clear on a response of placebo patients to taste disturbance. We don't really understand what that means. There are concerns in the active arm for unblinding, and this slide presents the 24-hour frequency by whether subjects experience taste disturbance. Gefapixant 45-milligram subjects who experienced this had the smallest geometric mean ratio in cough frequency at week 24 in Trial P030 or at week 12 in P027. How to interpret this is unclear.

DR. CARVALHO: The sponsor has their hand raised. Do you have discussion that's relative to the clarifying question? And if so, please go ahead.

DR. BOLLINGER: Yes, we would like to respond to the patient-reported outcome discussion, and Allison Martin Nguyen will come to the podium.

MS. NGUYEN: Yes. Thank you. I don't want to get into a back and forth with the agency on this point around the 3.3 and the 4.1 thresholds. What the issue was, the agency did share concerns that the 1.3 threshold did not seem appropriate to them based

on the anchor-based analyses that were conducted, and they didn't specifically ask us to look at 3.3 and 4.1. What the agency asked us to do, as part of our discussions at the late cycle review, were to revisit our phase 2 data with those analyses using the higher anchor of much improved and very much improved on the PGIC. And from that analysis, the 3.3 and the 4.1 thresholds were identified, and we did share those thresholds with the agency and indicated that we would rerun our analyses using those as a sensitivity analysis to the 1.3 threshold. So I just wanted to clarify that one point. Thank you.

DR. BOLLINGER: Yes. In addition, we would also like to have Dr. Dicpinigaitis address the questions about the relevance within the other domains.

DR. DICPINIGAITIS: Thank you, Dr. Bollinger. Peter Dicpinigaitis, pulmonary critical care physician. I opened my cough center 20 years ago, and since then, I've personally evaluated over 2400 chronic cough patients, and the discussion we're having here doesn't really reflect what I see and

what I'm told by my patients.

The psychological and social aspects of a persistent chronic cough are as important, and in many cases more important to the patient than the physical domain. Of course, the physical domain -- chest pain, urinary incontinence -- is very important, but patients tell me that their lives are ruined by the cough because they've become socially isolated. They haven't been to a restaurant, to concerts, or to church for 10 or 20 years. In fact, we did a study showing that 53 percent of the patients coming to see us test positive on a clinical depression scale. So my experience is that the social and psychological aspects of RCC/UCC are as important, if not more important than the physical domains. Thank you.

DR. CARVALHO: Back to the panel members.

Dr. Hamblett?

DR. HAMBLETT: Yes. Thank you. My question is for Dr. Philip. Nicole Hamblett. There was no discussion of adherence to study drug, and in particular among those with taste-related adverse

events that did not discontinue study drug, so I was hoping you can clarify that. Also, the protocol that was provided in a Lancet article seemed to prespecify a per-protocol analysis that presumably would provide an estimate of efficacy among those who tolerated and were fully adherent. So I'm wondering if you could speak to that as well as we consider these estimates of efficacy.

DR. BOLLINGER: Dr. Philip?

DR. PHILIP: Thank you, Dr. Bollinger.

If I understand correctly, your question begins with compliance to therapy or adherence to therapy, and what data we have to support numbers of patients who were appropriately taking therapy? Is that correct?

DR. HAMBLETT: Correct, yes.

DR. PHILIP: Of course, in our data, we collected the treatment compliance adherence, and as commonly seen in well-monitored clinical trials, about 95 percent of the patients were at least 80 percent compliant. There were no notable differences between the treatment groups in the

extent of exposure to the drug, and the exposure and treatment compliance in each study individually was consistent with the results that we generally present across the pooled data, which, again, approximately 95 percent of the participants were compliant.

You acknowledged, and we have discussed, that there are patients who discontinue therapy. Some of those patients do continue in the study so that we can continue to collect efficacy data maybe across all treatment arms, about a quarter of the patients, but in terms of the patients who were to be on therapy, whether or not they had a taste AE, they were compliant with therapy as long as they were continuously receiving therapy. Thank you.

DR. CARVALHO: Dr. Hamblett, does that answer your question?

DR. HAMBLETT: Sure. Yes.

Did you by chance do a protocol analysis that looked more carefully among those who tolerated and stayed on study drug?

DR. BOLLINGER: Yes. Dr. Hamblett, I'm going to have Dr. La Rosa answer this question.

DR. LA ROSA: Carmen La Rosa, clinical research. We did conduct per-protocol analysis, and the results were consistent with the primary analysis. Thank you.

DR. CARVALHO: Okay. We'll move on to the next panel member.

Dr. Coon?

DR. COON: Thank you. Cheryl Coon here. I appreciate the presentations by the sponsor and the FDA. I think that you did a really great job explaining how COAs are developed, evidence that's usually needed or requested, and how we then interpret data from COAs. There are a few pieces of information that I'm wondering if data on them are available, so I think that this question is for the sponsor.

First, did you conduct any qualitative interviews with patients to try to understand what would constitute a meaningful change in terms of their cough frequency or in terms of the PGIC?

DR. BOLLINGER: I'll ask Allison Martin Nguyen to speak to this question.

MS. NGUYEN: Thank you, Dr. Coon. We did conduct qualitative research, as I noted, to confirm the content validity of the LCQ. As part of that, we also did cognitive debriefing of the LCQ. We did not specifically debrief on the patient global impression of change; however, through that qualitative work, we did hear from patients through those interviews around their cough frequency, similar to what Dr. Dicpinigaitis mentioned, that total reduction to 100 percent of their cough is not something that they're expecting. But that was qualitative information; it wasn't quantitative per se.

I can show for those who are interested, if we can have slide up, to support the LCQ -- sorry. We need to get on to our system so I can show this slide. In terms of the LCQ, it has gone through a quite rigorous process of development and validation. As is standard in the scientific community around patient-reported development, it started with the literature review, reviewing what already existed in the literature.

As Dr. Birring noted, the qualitative concept

elicitation was conducted early on with patients with chronic cough, published in 2003. That went through an item reduction phase, where it looked at the impact factor method with 104 patients. They also conducted a psychometric study in that process, then the psychometric validation that we already talked about that was published by Raj.

We conducted the psychometric validation again, specifically in the RCC and UCC population that I noted was published in 2022, and then the qualitative interviews that we conducted at the request of the agency, where we interviewed another 20 patients specifically with RCC and UCC that were representative of the phase 3 population, and through that did the concept solicitation, and then also cognitive debriefing.

The culmination of all of that work, we are highly confident that this is a valid measure for assessing the the full impact of cough on patients lives. Thank you.

DR. HAMBLETT: Thank you.

In terms of additional evidence, do you have

cumulative distribution functions that show the change on the different PRO scores by the PGIC categories from your phase 2b study?

DR. BOLLINGER: Yes, we do. I'll have Allison Martin Nguyen return to the podium.

MS. NGUYEN: Yes. Actually, we have them from phase 3. If I can have slide up, this is the CDF curves of the PGIC. The same measure that was used in phase 2 was used in phase 3. You can see the 1.3 line that's shown here across all the PGIC categories.

We also have these curves just for Protocol 030 at week 24. If we can show that? Slide up, please. Again, this is Protocol 030, week 24, which was our primary time point for analysis. From this, we feel confident that the LCQ, those scores are tracking with categories of the PGIC. Thank you.

DR. HAMBLETT: Thank you.

Do you have these for cough frequency by chance?

DR. BOLLINGER: We actually do.

DR. HAMBLETT: Yay.

(Laughter.)

MS. NGUYEN: One second, till we pull that slide.

DR. HAMBLETT: Thank you.

MS. NGUYEN: Can I have the cumulative distribution curves, the CDF curves for 24-hour cough frequency in the pooled analysis? We do have that analysis. I'll take a minute here to find that, and I can bring that back for you. Thank you.

DR. HAMBLETT: Thank you.

And then the last CDF I was curious about is if you do have that for the treatment groups, so by the COA score, looking at the change in the score over time by treatment arm.

MS. NGUYEN: Allison Martin Nguyen. Sorry. We're still trying to pull that slide.

Can I have PR-36, please? Thank you. Slide up, please.

So I think this is what you're looking for, Dr. Coon. This is the CDF curve of the LCQ total score by treatment group in the Protocol 027 pool at week 24. On the vertical lines, you can see we have

lined the 4.1, the 3.3, and the 1.3 threshold. And essentially what this shows us is that the difference between gefapixant and the placebo group is obvious across a range of thresholds, not only at the 1.3, but also all the way up to the 4.1 threshold. Thank you.

DR. HAMBLETT: Thank you. I appreciate that.

Dr. Carvalho, I do have a couple more questions, but I know that we are time sensitive. So should I stand down and come back if we have time later?

DR. CARVALHO: Thank you for asking, Dr. Coon, and we'll come back to you. So go ahead and just raise your hand again.

Dr. Kelso, you're back on.

DR. KELSO: Yes. There was a question earlier about trying to assess the effect of the taste disturbance on the outcome, and it was answered once by the sponsor and once by the FDA, but using different metrics. The response that was given by the sponsor was to show us data in the placebo group about taste disturbance. Do you have that same data

for the treatment group?

DR. BOLLINGER: Yes, we do. Dr. Philip will return to the microphone.

DR. PHILIP: Again, remember the question of interest here is whether reporting the taste AE is impacting efficacy, and we have the confounding of both of these being pharmacologic effects of gefapixant that could travel together. What I showed previously was that in the non-confounder comparison between those with and without a taste AE in the placebo group, there was no evidence of greater efficacy present in those with the taste AE. We could expect, however, these effects to travel together in the gefapixant group -- slide up -- and what we see is that the same metric that you saw with the placebo group, now in gefapixant, improvement from baseline -- if we can bring the slide up for the cough frequency, please -- is numerically greater for gefapixant, 64 percent improvement from baseline versus 56 percent without a taste AE.

So as expected, a larger improvement from baseline, but if in fact reporting the taste AEs was

having a substantial effect on efficacy, we might have expected perhaps even a larger contrast between these two subgroups. What we see here clearly is a difference, but one that is easily explained by the activity of the drug.

In the broader context, to understand what we observed in our clinical program is clinically meaningful is the broader sense of what gefapixant versus placebo has generated. And stepping back to understand that we see efficacy meeting what we believe is the substantial evidence of effectiveness by looking at active versus placebo in cough counts, whether the original count or the recount, the data are very similar. Even if the p-value varies a little bit with the small variation in the actual effect size, broadly speaking, that effect is still present in both counts, and that effect is really the question that has been brought to the committee today.

FDA has mentioned that in the various PROs that we studied in our program, that these are not multiplicity adjusted, which is true of course, but

remember that the standard for approval of substantial evidence of effectiveness is not quite the same as the question that's being asked today. The reason why secondary endpoints are included in clinical trials, even if not statistically powered for a p-value, is to provide additional evidence to provide context for what efficacy is meaningful, and inform the interpretation of the primary and key secondary multiplicity adjusted analyses.

What we see when looking at the patient-reported outcomes, where patients are telling us what's important to them on endpoints that have been validated to be relevant to understanding their cough -- slide up -- whether or not in the presence of multiplicity adjusted p-values, what the patients are telling us on gefapixant versus placebo, it shows consistent benefit of gefapixant over placebo.

DR. KELSO: I'm sorry to interrupt, but this is not addressing my question. My specific question you did answer -- if you can bring that other slide back up -- is that in people who have the taste disturbance did in fact do better than those who did

not have the taste disturbance, and there's many possible explanations for that, but it leaves open the possibility that some of the tiny improvement seen overall in the patients receiving the drug could have been affected by this unblinding effect, is my interpretation of that. So you've answered my question. Thank you.

DR. PHILIP: I agree that there are many factors in play here. It can be hard to separate those factors. I think it is relevant to look at the data that maybe most cleanly answer this question, which is the data you saw previously in the placebo group, which does not suggest such a relationship as being active in this group, and we believe this supports, overall, the efficacy that's been demonstrated with gefapixant. Thank you.

DR. CARVALHO: Dr. Kelso, does that answer your question?

DR. KELSO: Yes. Thank you.

DR. CARVALHO: Next on the list is Dr. Courey.

DR. COUREY: Mark Corey, ENT. I think I'm

becoming more confused with the questions. The cough frequency, the absolute cough frequency change, was that compared with your anchor-based analysis questions? How does that relate to the -- as I see it, the 64 percent with the placebo, with the taste effect, had a closer response to the group as a whole than the people without the taste side effect, so it seems to be influencing the results, possibly.

What is the proposed mechanism of action? I thought I heard from the Merck sponsor presentation that the taste side effect didn't always last, and if the taste side effect went away, what is the mechanism proposed for the continued response to the medication for cough suppression?

DR. BOLLINGER: I'll ask Dr. Smith to respond to that question.

DR. SMITH: Thank you, Dr. Bollinger.

As someone who recruited patients to these trials, and therefore talked to many patients with taste AEs, you're absolutely right. Some of these taste AEs did settle down during the conduct of the trial, and I think the ongoing efficacy of the drug

despite that speaks somewhat to the taste AEs not mediating the effects here. Thank you.

DR. CARVALHO: Dr. Courey, does that answer your question?

DR. COUREY: Well, no. Well, it answers the question, but I might disagree with the response.

DR. CARVALHO: Any other comments?

DR. COUREY: No. Thanks.

DR. CARVALHO: Thank you.

Next is Emma D'Agostino.

DR. D'AGOSTINO: Thank you. Dr. D'Agostino. I'd like to go back to Dr. Kelso's line of questioning. I'm wondering if either the sponsor or the FDA has that same analysis parsed by who did and didn't experience taste AEs, but with the PROs. It could be the LCQ analysis on any of the PROs, but if we could see any of the analyses by who did and did not experience taste AEs.

DR. BOLLINGER: We do have that data.

Dr. Philip?

DR. PHILIP: Thanks, Dr. Bollinger.

Following the logic that you heard me discuss

before, let me bring up the data you're asking for in the placebo group first. We do have both the objective cough counting, as well as the subjective measure, and in this case our key subjective measure being the LCQ; in the placebo group, first, please, so that we can have that comparison unconfounded, and then I will also show you the efficacy in the gefapixant group on the subjective endpoints.

Yes. Slide up, please. This slide adds to what you saw previously, already shown -- build it, please -- was the 24-hour cough frequency, and now added is the LCQ total score, here expressed as the proportion of responders. We have both the 24-week and 52-week time point, and what you see is essentially some flip-flop between the proportions reporting larger proportions of responders with versus without the taste AE, so clearly no clear evidence that having a taste AE somehow is driving efficacy as judged by the patient, even on this subjective endpoint.

We turn now to the gefapixant arm, looking at the LCQ responders again. Slide up. Now, we're

looking at proportions of responders, again week 24 and week 52. Here with the drug effect present, we see evidence of efficacy, as well as a relatively large proportion of patients reporting the taste AE. In those with the taste AE, a somewhat higher proportion were responders versus without at both time points. But again, if having a taste AE had a really substantial effect on the patient's perception, or even expectation that they were getting active drug that would affect how they complete their subjective scores on the LCQ, we might have expected larger than these essentially single-digit differences between proportions. Thank you.

DR. D'AGOSTINO: Thank you.

Can I ask one more quick question on the taste AEs? Can you tell me a little bit more about how these taste AEs manifested? I know we talked about what they were classified as, but is this while you're eating? Is this experience 24 hours a day? What exactly are these symptoms? I know we talked about how often they resolved and how quickly they

resolved, but how is this going to manifest in daily life?

DR. BOLLINGER: Yes, Dr. D'Agostino. I'll ask Dr. Willis to come to the podium for that description.

DR. WILLIS: Thank you. English Willis, clinical safety and risk management. What we know of the taste-related AEs is that they do appear early on and soon after taking the drug, at about day 2. We also know that of the patients who reported a taste-related AE, they reported them as mild. In looking at the duration, most of the patients maintain their taste-related AE for a duration of about 194 days.

We also know how they describe them, and the description of the taste-related AEs were primarily a salty, bitter, or metallic taste. We also know that patients from the data, that 25 percent of the patients resolved their taste-related AE around 65 days into treatment. In terms of the information of association with food, that information was not collected during the trials. Thank you.

DR. CARVALHO: I see that the FDA has their hand raised. Are there any comments for us now?

DR. CHIN: Yes. This is Stacy Chin, FDA. We just wanted to provide our perspective on the taste disturbance AEs and the potential impact on the interpretation of the efficacy results.

Both we and the applicant have looked into it, and how both the gefapixant group and placebo group who did or did not have taste AEs responded on the various endpoints, and our take-away is that it's an unquantifiable uncertainty. We just do not know how that may have impacted potential unblinding or bias in this study, and in our mind, it takes on more importance because the treatment effect size is rather small between the placebo and gefapixant groups. Thank you.

DR. CARVALHO: Thank you.

Next is Dr. Rank.

DR. RANK: Hi. Matt Rank. Thanks to all the excellent presenters. Thanks, Dr. Carvalho. My question has to do with another thing related to potentially uncertainty in evidence, and it's related

to the dropout rate in the trials, the two pivotal trials. I noticed it looked like the dropout rates exceeded 20 percent by a little bit in both trials, and that there was differential dropout rates.

My question for the FDA, the statistical and various analyses that you performed, were they sufficient, do you believe, to reduce concerns about this potential impact on the certainty of evidence of these trials?

DR. CHIN: Stacy Chin, FDA. I'm going to summarize your question. You would like us to comment on whether the relatively high dropout rate of greater than 20 percent or so had any impact; whether that missing data had any impact on the analyses. I will turn this question over to our statistical reviewers.

DR. RANK: Dr. Chin, that's correct, and also the differential dropout rate of about 10 percent in the arms. Thank you.

DR. CHIN: Thank you for clarifying.

DR. Y. KIM: Okay. Thank you for the question. I'm Yongman Kim, statistical team leader.

Would you bring up slide 66, main slide 66? And while we're waiting for the slide, I will quickly answer the question. The significant imbalance in treatment discontinuation between the 45-milligram and placebo did not lead to the same degree of imbalance, and we've seen this at the landmark time point, which was 28 and a half percent for 45 milligram and 15 percent for placebo.

Would you bring up backup slide 86? For the initial or high treatment discontinuation rate, 28.5 percent in the gefapixant group was reduced to 21 percent in terms of missingness, so we think this may be due to the continuing of the data collection after treatment discontinuation, so the missingness imbalance may be reduced. We conducted a sensitivity analysis, and it supports the primary analysis shown, as shown in the tipping-point analysis.

Did I answer your question?

DR. RANK: Can you repeat the last thing you said just one more time, please?

DR. Y. KIM: Yes. Our sensitivity analysis and applicant's sensitivity analysis, including

tipping-point analysis, supported the primary analysis results.

DR. RANK: Thank you. Yes, you answered my question.

DR. Y. KIM: Thank you.

DR. CARVALHO: Thank you, Dr. Rank.

Also, the sponsor has their hand raised. If you could make a comment.

DR. BOLLINGER: That may have been for a follow-up to one of the previous questions.

DR. CARVALHO: Would you like to proceed with that?

DR. BOLLINGER: Not at this point. Thank you.

DR. CARVALHO: Sounds good.

Dr. Kim?

DR. E. KIM: Edwin Kim, allergy and immunology at the University of North Carolina. I have a question for the sponsor. I'm trying to understand the placebo effect, and there was a slide that showed that a strong placebo effect is a known thing in trials like this, and I think a couple of

other trials were shown. Just understanding, in this study, many patients had these symptoms for over 10 years, and seemingly have been on other therapies without efficacy, and then somehow on placebo are having objective improvement in cough, up to 50 percent decrease.

Is there an understanding in the field or with the sponsor of what that mechanism might be? Because again, the difference between the gefapixant and placebo is not very large, so I do think it's important to try to understand where this placebo effect is coming from.

DR. BOLLINGER: Yes. Dr. Kim, Dr. Smith will respond to your question.

DR. SMITH: Thank you, Dr. Bollinger.

Jackie Smith, pulmonologist from the University of Manchester. So the way we understand the placebo effects in these studies, a great deal of it comes from other therapeutic areas, but there is some evidence in cough as well.

Slide up, please. Thank you. The placebo effect, as we understand it, is multifactorial, and

there are probably three main things to mention. There is some non-specific factors about being in clinical trials that improve patient symptoms, but the other two m in ones that we think are important here, that may have increased between phase 2 and phase 3, are the expectations of the patients and regression to the mean.

So what we know about the neuronal pathways that mediate cough include the central nervous system, both cortical and subcortical areas, and we have evidence in patients and in healthy controls that there are descending inhibitory pathways present in this patient group, and even in a healthy cough reflex, which are capable of inhibiting cough in response to cognitive processes such as expectation.

I understand the concern that these patients have been coughing for 10 years and not responded to previous other treatments, but I think we have to put this in context in that patients were enrolled to these studies with the knowledge that previous trials had shown positive findings in patients just like them, who hadn't responded to previous therapies. So

I think the level of expectation here is that the first therapy that is going to work for your refractory and unexplained chronic cough did have an effect here.

Then the last thing I think I should mention is regression to the mean. The patients recruited into the phase 3 studies had a greater severity of their cough compared to the phase 2b. So on the Cough Severity Visual Analog Scale, their severity was scored at approximately 70 millimeters, so that increases the possibility of some of the effects we see in the placebo-treated arm being due to regression of the mean. Thank you.

DR. E. KIM: Thank you for that explanation, and I bring it up because the 60 percent reduction that's been showcased is exciting. At the same time, in the clinic, if they're not enrolled in clinical trials without these expectations and some of these other factors, I wonder if that's a realistic expectation for those patients. That's all my questions. Thank you very much.

DR. BOLLINGER: Can we follow up with that,

Dr. Kim, please?

DR. SMITH: So if I could just respond to that, I think the way that we expect gefapixant would be used in the clinic would be in the same patient group that have been recruited to these phase 3 trials, and I wouldn't anticipate that the expectation of these patients outside of a clinical trial is going to be any less than it was within these trials, with the knowledge that this drug has been previously shown to be effective.

If it's ok, I'd also like to just take the opportunity to talk a little bit about the effect size. What patients are experiencing in these studies is, as you say, there's 60 percent drop in their cough frequency, and I note that the agency has some concerns that this is not a large drop over the placebo and have looked at the absolute change in cough frequency of just 1 to 2 coughs per hour.

I think there are two points I'd really like to make about that. First of all, when you talk to patients about their cough and steady cough frequency, it becomes apparent that patients don't

really think of their cough in terms of 1, or 2, or 5 coughs per hour. They're just not aware of that. They perceive improvements in their cough based on their reduction relative to their baseline. And as we've heard already, the baseline cough frequencies in this patient group are quite variable.

So people with very high cough frequencies may not notice a reduction of, say, 5 coughs per hour if they started off at 50 coughs per hour, but if you start off at 10 coughs per hour and reduce by 5 coughs per hour, you really notice that because it's a 50 percent improvement.

So we would very much support the use of percentage change as opposed to absolute reductions in cough frequency as being an important endpoint, or the most important endpoint, to look in these studies. And that's corroborated by some of the data that Allison Nguyen showed you earlier, that this has a much stronger correlation with the patient global rating of change than we saw with absolute change.

Then the second thing I'd just mentioned is that even if we do focus on the 1 to 2 coughs per

hour, I think it's really important that we don't underestimate the impact of that for patients. Patients don't see a reduction of 1 to 2 coughs per hour. The bulk of this coughing is actually occurring during waking hours, so it's concentrated within the day, and they don't cough evenly in that way. They cough clustered together in bouts that are really unpleasant, and it's those prolonged bouts that lead to people having to leave the room when they're in a meeting or have an episode of urinary incontinence. If you can shorten those bouts by a little bit or knock out some of those bouts, that can just make enough difference to a patient that they're going to appreciate an improvement in their quality of life. Thank you.

DR. CARVALHO: We have about five minutes left, so first I'd like to ask the FDA if they have any comment to what's been discussed. If not, we'll move on.

DR. CHIN: This is Stacy Chin, FDA. We recognize that the baseline cough count frequency does have a role in the perceived benefit in the

reduction of cough. That being said, what we are seeing is a pretty small difference no matter where you look across the responder curves and thresholds. So that's our main question for the committee, is we're seeing these small differences across endpoints with this potential unblinding issue and is that meaningful. We don't want this to get too much in the weeds of a discussion of methodological concerns or content validity issues. It's really, are these small differences meaningful and perceptible to patients. Thank you.

DR. CARVALHO: We will move on to Dr. Coon.

DR. COON: Thank you. Cheryl Coon here. I think my question actually flows really well from the last question, which is to the sponsor.

Can you put into words how a healthcare provider might convey the treatment benefit to a patient when looking at the relative reduction in the geometric mean ratio? I ask that because the primary endpoint is a very complex statistical endpoint, and ultimately that information has to be conveyed to the patients to make treatment decisions with their

healthcare providers.

DR. BOLLINGER: Absolutely. I'd like to call Dr. Dicpinigaitis to the podium, who has these conversations with patients every day with off-label use of medications. So I'd like for him to share his perspective on how he would talk to patients about gefapixant.

DR. DICPINIGAITIS: Thank you, Dr. Bollinger.

As I mentioned before, patients aren't coming in with an expectation that it will eliminate all cough. They want their cough just to, if possible, be in the background as opposed to the foreground of every minute or every hour of their waking day. So there's no demand or expectation for 100 percent reduction. There's just enough to change their quality of life. And as we mentioned before, coughing 6 times an hour versus 12 times an hour may make a person comfortable enough to go out in public to a restaurant or concert. Urinary incontinence is almost invariably due to a bout of severe coughing. You'd only have to minimize the severity or length of that cough to possibly even eliminate urinary

incontinence.

So patients aren't looking for a complete elimination of cough, but just enough to change their quality of life. And I can say that when we do improve cough by 25-50 percent, as rated by the patients, that translates often into a significant degree of satisfaction by the patient. Thank you.

DR. CARVALHO: We've got only about a minute left, so I'd like to ask Dr. Courey to ask his question.

DR. COUREY: This is to Dr. Smith. Were there any other co-therapies applied simultaneously during the trial period? In other words, we do a lot of cognitive behavioral therapies with our patients, and we have an 85 percent reduction in cough from that alone.

DR. BOLLINGER: Dr. Smith?

DR. SMITH: Thank you, Dr. Bollinger.

So within these studies, patients weren't receiving other treatments to address their refractory or unexplained chronic cough. Many of the more specialist centers like yourselves do cough

control therapy, which has been shown to be beneficial in a small number of trials, but patients couldn't be included in these studies that couldn't be commenced or couldn't be started within, if I remember correctly, about 3 months of the start of the trial. So those sorts of therapies, we're not having an influence on any of the effects seen here.

Does that answer your question?

DR. COUREY: Yes, to some extent. I mean, we never know exactly what about the CBT therapies help the patients --

DR. SMITH: True.

DR. COUREY: -- so even just their presence --

DR. SMITH: Exactly. They're complex interventions, and whilst we've seen in double-blind, randomized-controlled trials that that they can reduce cough frequency by about 30 to 40 percent, we don't really know what components of those therapies are making the difference there, and there are multiple components to them.

DR. COUREY: Is it just being in the room

with the clinician who seems to care?

DR. SMITH: Probably not because the control trials have used sham therapies, so they have had the same sorts of contact with healthcare services, so it's probably not just that.

DR. COUREY: And just one follow-up. On the proposed mechanism, whereby they both work on the P2X3 pathway, I'm still confused on how if the taste abnormality goes away, the cough suppression continues. I just can't --

DR. SMITH: Sure. So in terms of the mechanism of action, we believe the antitussive effects, P2X3 ion channels on the sensory nerves present in the airways that are controlling cough. The taste side effects are due to slightly different channels.

Based on animal models, we believe they're heteromeric channels, so these channels have a mixture of P2X3 and two subunits. So they're a little bit different, and they are found on the nerves that are renovating the taste buds. So gefapixant is modestly selective for the pure P2X ion

channels that we think mediate cough over those heteromeric channels.

As I said before, as we saw in the study, yes, a number of our patients had their taste AEs settle down during the study, and if that were mediating the treatment effect, what I would expect to see is the effect of gefapixant waning over time and coming closer to placebo, but that is not what the data tells us. So it would appear that those patients whose taste AEs went away maintain the efficacy of the drug.

DR. COUREY: Thank you.

DR. SMITH: You're welcome.

DR. CARVALHO: Thank you to the panel, to the sponsor, and to the FDA. We will now break for lunch. We're going to reconvene at 1:30. Panel members, please remember there should be no discussion of the meeting topics with other panel members during lunch.

Additionally, we should plan to reconvene at around 1:20 pm to ensure you're connected before we start the meeting again at 1:30. Thank you,

everybody.

(Whereupon, at 12:42 p.m., a lunch recess was taken, and meeting resumed at 1:30 p.m.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

Open Public Hearing

DR. CARVALHO: Welcome back, everybody. We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

For today's open public hearing, each presenter has been allotted three minutes for their

presentation, and I apologize in advance that I may have to stop it at three minutes or just a few seconds beyond because we have a long number of speakers. Thank you for your cooperation.

Speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MS. KAPLAN-SEIDE: Good afternoon. Thank you for allowing me to speak today. My name is Gloria, and I am a patient and have not been compensated for my remarks. I have had a chronic cough for 8 to 9 years. What I can tell you is it can come on at any time, including in the shower; sitting or driving in the car; when I am preparing food or eating a meal; having a friendly conversation or speaking to someone on the phone. I used to laugh a lot; now, I'm apprehensive to watch a comedy because I may want to laugh, and laughing will make me cough. Coughing for 4 to 5 minutes rattles my body and my personality. Lately, if I cough, I'm afraid I will

move my bowels.

When I began coughing, I went to a pulmonologist, an ENT, and gastroenterologist. I was referred to an allergist and a speech pathologist. I don't have allergies and the speech pathologist wanted me to increase my pitch. I went to an acupuncturist and a naturalist. I followed a food plan and lost 20 lbs; still no relief. I had a pH capsule attached to the distal esophagus. There was no significant correlation between cough or reflux.

Finally, I changed to a more expensive health insurance plan, so I'm able to see doctors at the Cough Clinic at Cleveland Clinic. The medication prescribed brought some relief for a few weeks, then the cough broke through to its usual level. I wanted relief. In July and September this year, I had injections in both sides of my neck. The shots were worthless.

My occupation the last nine years is to assist people. It is a telephone position, speaking constantly to customers for 7-and-a-half hours a day. Can you imagine speaking to someone, and without

warning cough uncontrollably? I can barely ask them to hold while I grasp for a long drink of water, relax my body, regain my composure, and continue my conversation. The only thing that helps me is drinking water, and anytime I leave my home, I have to know where a bathroom is located.

I am suffering with chronic cough every day. I don't cough once or twice a day, but at least 15 to 20 times a day. Each occurrence can be wrenching, taking away my energy. This affects my spouse, my children, my grandchildren, my family, and friends. Plus, when I go to the grocery store, I wear a mask. Sometimes I hunch over and cough relentlessly in the stores as if I were Quasimodo. I can't tolerate the coughing anymore. Sometimes I wonder if coughing will affect my longevity. Please, I need treatment. Thank you.

DR. CARVALHO: Thank you very much.

MS. KAPLAN-SEIDE: You're welcome.

DR. CARVALHO: Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state

your name and any organization you are representing for the record, and you have three minutes.

DR. PETERS: I'm Anju Peters. I'm an allergist at Northwestern. I actually submitted a PowerPoint, if that can come on also. Thank you very much. I take care of lots of patients with chronic cough. My disclosures, Merck has funded some of our research in chronic cough, and I've participated in two advisory boards.

We know what chronic cough is, which is cough present for more than 8 weeks. Refractory is if cough is associated with other underlying conditions but persisted despite treatment of those conditions. And then unexplained chronic cough is cough for which we've not found the condition and continues to be present.

This is a qualitative study that we participated on. Many of my patients reported on this, and this was looking at the impact of chronic cough, which is in blue, and unexplained chronic cough, which is in green, and total chronic cough is in orange, on daily activities. As you can see,

starting from the left, chronic cough has significant impact on patients' daily activities, including their ability to communicate, sleep, including their partners can't often sleep, and plays a role in their relationships. People feel stigmatized from cough, as we just heard, so it does play a huge role on daily activities.

In addition, what this study showed that we participated in is patients with chronic cough often are very frustrated. More than half of them will say that they're embarrassed by their chronic cough, they're always afraid, they never know when the cough will come, and it has, again, a significant negative impact on their quality of life.

This is a study from the UK where they did a survey on patients with chronic cough. Chronic cough is in blue. Gray is those individuals who don't have chronic cough. And as you can see by the arrows that I put in this slide, patients with chronic cough are more likely to report having depression compared to those without chronic cough.

In this survey, what they also looked at is

the impact of chronic cough and people's ability to work, as we just heard. Chronic cough patients are more likely to miss work because of their cough, and even when they're at work -- presenteeism -- they are impaired because of their chronic cough, and overall their impairment is higher at work compared to those without chronic cough.

And finally, this was a study that we did at Northwestern, looking at our patients with chronic cough who come to their primary care physicians, and as you can see on that graph, they've had more than 4 to 6 visits with their primary care physician and continue to cough. They're often prescribed or by themselves take multiple medications, which can have side effects, including antibiotics, steroids, opiates, et cetera, without benefit to their chronic cough.

So in conclusion, I've shared with you just a little bit in terms of chronic cough. It has a significant negative impact on quality of life. These individuals are more likely to report depression. It leads to work productivity loss. It

affects them every day. They try many medications without relief. So in conclusion, chronic cough has a significant burden on our patients, and these patients deserve some treatment. Thank you.

DR. CARVALHO: Thank you very much.

I believe that speaker number 3 is not here, so we'll go on to speaker number 4. Please unmute and turn on your webcam. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you are representing for the record, and you have three minutes.

MS. OLEKSIUK: Good afternoon, esteemed FDA advisory panel. My name is Mary Oleksiuk. I am 61 years young, a patient living with chronic cough. I have no conflict of interest, and I'm not being compensated. I am just delighted to be speaking with you today.

I have been coughing for a little over 4 years before I started my 18-month medical journey to being diagnosed with chronic cough. My daily life challenges included coughing uncontrollably, leading to intense chest, rib, and pleura pain. I stopped

eating at restaurants, as my coughing would cause a scene. I had a hard time keeping conversations with family and friends, as I would have horrible coughing fits. I had difficulty completing a Pilates class, and it was impossible to go to the gym.

In January of 2019, I knew I could no longer ignore my symptoms when I had started coughing so uncontrollably that I would vomit multiple times a day, every day. This uncontrolled cough had an enormous impact on my physical health; mental health; family life; daily professional life; social life; diet; and the ability to travel.

At the time, I was an executive, the chief human resources officer at a Fortune 100 company. During critical strategy, executive team, and board meetings, I was told that I was disrupting participants' decision-making skills. My coughing was so completely distracting and derailing meetings that I was asked to continue to participate in the meetings from my office and to just please keep myself on mute. I was mortified because at the time I just couldn't perform and make a professional

impact in my role that I knew I could have. Everyone was extremely kind and sympathetic. Everyone had many suggestions on which doctors I should consult for my coughing condition.

Just as COVID was starting to get attention, I needed to fly to San Francisco. My cough was completely uncontrollable for the entire flight back. Flight attendants gave me any and as many blankets as they could find, and just asked me to please cover up and try to muffle my cough, as I was distracting everyone around me.

My cough was very hard to diagnose. It took about a year and a half. I needed to take time off from work to seek medical help. Every doctor and specialist I saw were pretty sure I had whatever was their specialty, as my cough had spun off many side symptoms that seemed to point to bronchitis; pleuritis [ph]; pneumonia; whooping cough; asthma; GERD; and I was prescribed different medications, treatments, and protocols that didn't help and sometimes made the coughing much, much worse.

I underwent many tests, procedures, and

medications before getting an accurate diagnosis of chronic cough and a treatment plan. I learned through careful monitoring that my chronic cough is triggered by so many common everyday items: chocolate; flaky food; very dry conditions; cold temperatures like opening the refrigerator; as well as cold foods; ice cream; ice; drinks, just to name a few. I've learned a lot in my journey and am extremely grateful to my doctor at the Cleveland Cough Clinic for helping me diagnose my chronic cough and helping me get my life back on track. Thank you so much for listening to my story. I appreciate your time.

DR. CARVALHO: Thank you very much.

Now, speaker number 5, please unmute and turn on your webcam. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you are representing for the record, and you have three minutes.

DR. GROSS: Good afternoon. My name is Gary Gross. I'm representing myself, and I'm not being compensated for my time. My first clinical trial was

done in 1978 when I was on the full-time faculty at UT Southwestern Medical School, in the pulmonary division working with Alan Pierce. When I was not aerosolizing bacteria into mice to investigate mechanisms in pneumonia, I treated and taught about asthma. My first trial looked at terbutaline as a bronchodilator. I have continued to do clinical research, having completed over 400 studies. I'm an adjunct professor of internal medicine at UT Southwestern and continue to teach.

My interest in chronic cough began in 2015 when Afferent was looking at the molecule under discussion today. I had a few patients who had chronic cough and had tried everything available suggested by the literature. One of my patients, a dentist whose husband is an MD, had tried multiple cough centers, including UMass, and she continued to cough.

The original study we did was a crossover, and it was apparent to the staff and patients, when they were on the active crossover, that patients described those periods of relief as much better or

wonderful when completing their diaries. VAS scores went from 75 to 48, 51 to 1, and 74 to 1. The patients not only reported improvement, but related that family members, friends, and colleagues also noted improvements in their cough.

I've conducted about 13 chronic cough studies, and the P2X3 antagonist molecules have shown the most consistent benefit. I believe that chronic cough is a heterogeneous disease. Some patients with chronic cough may not respond to this molecule, but may respond to other antagonists under investigation. If the population studied is heterogeneous and not enriched for the outcome you are measuring, it is harder to see a response in mean data. The outliers at the ends of the distribution curve may be missed.

There is no way to enrich this population for P2X3 responders because there are no clinical markers. If anything, the population studied was deprived of the good responders because an exclusion criterion of the pivotal trials was prior exposure to the molecule. The center still had to enroll an average of 6 patients per trial, potentially using

less than ideal patients. Despite this obstacle, the studies met the primary endpoint, and even after data manipulation, one study continued to meet statistical significance while the other was just over the p-value of 0.05 for the primary endpoint.

I think the body of evidence, including the early studies with this molecule, then two larger studies, clearly show a benefit for some patients with chronic cough and have no other treatments available. The characterization of chronic cough is a symptomatic condition and minimizes the suffering of these patients, as Peter previously noted.

One of our patients cried when we had to reclaim her drugs after the Afferent study, the first drug that afforded her relief and a normal life. Another patient is estranged from her daughter because her daughter thinks mom could stop coughing if she really wanted to. We have a patient who delivers cars for his company. He passed out while coughing on a drive from Abilene to Dallas. There are many other patient reports of isolation and removal of social events due to their cough, as

previously mentioned.

In my opinion, not only is this an ideal first drug to be approved for chronic cough because of its efficacy, but also because of the taste effect. I recognize, as you do, that clinical trials differ from actual practice. The patients who have a significant benefit from gefapixant will continue to take the drug despite the inconvenience of some taste effect, while the patients who did not derive this benefit will discontinue the drug. If it is not approved, not only will patients unnecessarily suffer from cough, but other pharmaceutical companies may redirect their resources to other drugs which have an easier path to approval. This outcome would be harmful to patients and potential future discoveries in the field of chronic coughs. Thank you.

DR. CARVALHO: Thank you very much.

Speaker number 6, please unmute and turn on your webcam. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you are representing for the record, and you will have three minutes.

MS. SHAW: Hello. My name is Carol, and I'm almost 68 years old. I'm a patient, and I have not been paid to speak here today. I've had a chronic cough for approximately 35 of my 68 years. This has caused me much embarrassment; frustration; discomfort; fear; and guilt in my work, home, and social lives through those 35 years. I feel terrible for my supportive husband and now grown kids who have had to listen to and worry about me coughing at the slightest irritation, which includes speaking; eating; showering; breathing in air conditioning; getting up from reclining; et cetera; or randomly with no known cause. I've always been afraid of getting through meetings; my kids' recitals; weddings; funerals; plays; movies; grocery stores; et cetera, without coughing, and have had to leave on occasion to get through a coughing fit.

I've seen pulmonologists; gastroenterologists; otolaryngologists; speech therapists; and my primary care physicians over the years. I've had numerous diagnostic procedures, including endoscopies; esophageal manometry; asthma

spirometry and [indiscernible] tests; barium swallow tests; chest X-rays; and I'm awaiting another endoscopy to test esophageal strength. None of these tests have found a treatable reason for my cough.

Through the years, I've tried gabapentin; amitriptyline; various inhalers; allergy pills and nasal sprays; neti pots; speech therapy; numerous GERD medications; over-the-counter cough medicines; superior laryngeal nerve injections, Tessalon Perles; and recently Lyrica, all to no avail. Gabapentin was the only drug that seemed to work. Unfortunately, my cough crept back in along with some side effects. If the gabapentin had continued to help my cough, I would gladly have chosen to live with the unfortunate but manageable side effects versus the cough.

I've had many major surgeries and a widowmaker heart attack with a stent placement for which I was given morphine because tramadol makes me violently ill. Morphine I found is the only drug that stops my cough. Two weeks ago, I had anterior cervical discectomy and fusion surgery with an incision in the front of my neck. Once off the

morphine, my cough returned, causing increased severe pain near the incision, and it irritated my esophagus even further in the following weeks. Unfortunately, morphine is not a sustainable treatment.

I'm afraid I've nearly exhausted all treatment options and would love to help find an effective treatment for me and, as I've recently discovered, so many others dealing with chronic cough. Until my doctor mentioned this hearing, I thought I was alone, so thank you very much for letting me speak today, and I wish the project good luck. Thank you.

DR. CARVALHO: Thank you so much.

Speaker number 7, please unmute and turn on your webcam. Will speaker number 7 begin and introduce yourself? Please state your --

MS. SAKS: Hello. My name is Joan Saks.

DR. CARVALHO: -- name and any organization you're representing for the record, and you have three minutes. Thank you.

MS. SAKS: My name is Joan Saks. I am a patient, and no one is paying me. I'm here to tell

you what my journey has been like coughing for 50 years. It's embarrassing, it is exhausting, and when I can't catch my breath in a real coughing fit, it's absolutely scary because I'm afterwards trying to inhale and gasping for air. The only thing that has helped me after all the tests -- and as the speakers before me have indicated, I have had all those tests: the allergy tests, the cameras down my throat, the endoscopies, the sinus scans. Nobody can find a reason for my cough.

The only way I lead a normal life is through codeine cough medicine, and I'm afraid to take it because of all the side effects; and I therefore take it, but you have to if I want to go to the symphony. You're not allowed to cough at the symphony; if you get on an airplane. Other than that, you're coughing in a public place, and as I'm choking, I can see people getting up and walking away because they don't want to be near me. At night, I sleep sitting up, and cough and cough until I take pity on my husband and go into another room.

So if there's a medicine out there that would

actually take away my cough that I can live with and not have to cough all the time, that would be a fantasy. My fantasy would be able to sleep laying down with just a pillow and going to a concert where I know I've taken cough medicine so I can sit there and not sleeping for the first half hour of that concert because the cough medicine knocks me out. So I thank you for listening to me. And yes, any drug that can help and not be an opioid would be very, very wonderful. Thank you for listening.

DR. CARVALHO: Thank you very much.

Speaker number 8, please unmute and turn on your webcam. Will speaker number 8 begin and introduce yourself? Please state any organization you are representing for the record, and you have three minutes.

MS. McDONOUGH: Hi. I'm Mary Ellen McDonough, and I'm a patient with chronic cough. I am not being compensated for my remarks today. My journey with a chronic cough began about five years ago, and this condition has affected every area of my life. By profession, I'm a registered nurse,

recently retired, but I worked in the neonatal intensive care unit and the pediatric intensive care unit, and there were times when I questioned whether my cough would affect the well-being of these kiddos. It was pretty scary, and I also had colleagues that questioned that since I could not get a diagnosis.

Because of the persistent cough and the resulting sleep deprivation, I was afraid that I might make a medication error or forget to do something important at work. I was prescribed cough medicine with codeine to help me sleep. Obviously, this is not a long-term solution. I had numerous visits with ENT doctors and pulmonologists. These visits included CAT scans; MRIs; multiple laryngoscopies; and endoscopies.

I was treated with numerous doses of antibiotics and antifungals. I was frequently on high-dose steroids. The use of steroids is not without its own complications. I had three episodes of aspiration pneumonia due to my coughing. In addition, I made countless visits to my pharmacy, hoping that something, anything, would help, and I

still have no diagnosis or hope of one.

It felt like there was always a lump in my throat, and my throat felt like it was on fire. People complained of difficulty hearing and understanding me. My voice was extremely hoarse. Because of this, I limited my social activities. The unpredictable nature of my cough in both frequency and severity led to both embarrassment and anxiety. I was not only frustrated, but I was also really, really scared. During the time I was looking for a diagnosis, my brother was in treatment for esophageal cancer and subsequently passed away. The thought that I may have cancer was always in the back of my mind.

As a medical professional, I feel confident navigating the medical system. I also live in Boston, a medical mecca, and am perseverant. Even so, I was unable to find any help for this problem for five years. I wonder whether or not a layperson would go to such lengths or simply give up. My hope is that in sharing my story with you, other folks will not go through having that costly and

debilitating course that I have had.

I finally found a wonderful ENT doctor here in Boston who diagnosed my chronic cough. He wasn't surprised by it. He identified a paralyzed vocal cord, which was treated with a Silk injection. I worked with a speech therapist and I adhered to a reflux diet. Despite this, my cough continues today, and I wish there were a medication that could help. Thank you.

DR. CARVALHO: Thank you very much.

Speaker number 9, please unmute and turn on your webcam. Will speaker number 9 begin and introduce yourself? Please state state your name and any organization you are representing for the record, and you have three minutes.

MS. BAMBRICK: Hello. My name is Marlene Bambrick, and I have been a chronic cough patient for 44 years. I'm a retired nurse, and I worked as a care coordinator and registered nurse first assistant with colorectal surgeons for a majority of my career. I am receiving no reimbursement for this presentation, and I have no affiliation other than

being a patient.

When my cough was bad and I would be assisting in surgery, I would have to break scrub because I couldn't stop coughing, have hot herbal tea, a cough drop, and over-the-counter cough medicine. Once I was scrubbed back into surgery, I would pray that I would not start coughing again until the operation was complete.

In the outpatient office, I would have to excuse myself from patient exam rooms to go through my routine of trying to stop coughing. When I was on the phone with patients, I would have to put them on hold. I have had to step out of wedding and funeral ceremonies due to the intense nature and disruptiveness of my cough, and it was embarrassing.

In the early '80s, I underwent a full evaluation, which included ENT; pulmonary; allergy; GI, and had multiple tests that others have already mentioned. I was finally diagnosed and treated for asthma and reflux. I still had intermittent periods of coughing and would be put on a high steroid taper, which sometimes would last 1 to 3 months. A friend

suggested I see the Institute for Functional Medicine, which I did, and they suggested an elimination diet. I was prescribed multiple supplements so I could stop taking the reflux medication; exercise; stress reduction; yoga; meditation; and counseling, all of which some of those I had been doing, and I started doing all of them with some minimal help. I also tried acupuncture and FSM, which I found was very very helpful.

I was finally, after another number of years, referred to a pulmonologist who specialized in chronic cough, who ordered another full evaluation, including a lung biopsy. The lung biopsy showed that I did not have asthma, and I was taken off all my asthma medicine and labeled a hypersensitive cough syndrome patient. This was during the time when the opioid epidemic precipitated rules and regulations regarding narcotic medications, including cough medicines. I saw a speech pathologist, who gave me breathing and vocal exercises to suppress the cough, and despite all of this, and treatment, I still have

periods of intense coughing.

My hope is that this presentation will help you understand the intense challenges of being a chronic cough patient, and you will take this knowledge into consideration in your decision making. Thank you for your attention.

DR. CARVALHO: And thank you so much.

The next speaker is speaker number 10. Please unmute and turn on your webcam. Will speaker number 10 begin and introduce yourself? Please state your name and any organization you are representing for the record, and you have three minutes.

(No response.)

DR. CARVALHO: Is speaker number 10 available?

MS. BUCHTER: Yes. I'm trying to find the camera.

(Pause.)

MS. BUCHTER: Very good. Thank you for this extra time.

Good afternoon. My name is Suzanne Buchter, and I am a retired administrative assistant from a

local hospital in Norfolk, Connecticut. I would like to thank you for selecting me to speak at this very important open hearing to share my journey as a chronic cough patient for the past 28 years. I am voluntarily speaking, and I am not getting paid to speak.

After reviewing my life with this cough, I have decided to share the most impactable times, not to lessen the other emotions. I have traveled several hours to see doctors, from Worcester, Mass, to the Bronx, New York, while living in [indiscernible], Connecticut. In 2015, I was on a high dose of gabapentin, which led to intestinal globules, which required emergency surgery. The doctors had to immediately discontinue the gabapentin, which led to 2 seizures and were treated as a code blue, and I was transferred to ICU for several days and developed ICU psychosis.

I was recently diagnosed with bronchiectasis, and the doctor said this was caused by my heart. In August of 2023, due to the intensity of the cough, I developed intense headaches due to low spinal fluid

pressure. I was evaluated by doctors, and they informed me my severe coughing led to the intense headache and a spinal fluid leak, which was treated by a blood patch. I have found it hard to function a normal life, which leads to a terrible quality of life for me, my husband, and my family. Even after all these years of coughing, I still have the feeling of embarrassment when I am out in the public. I find it difficult to attend funerals, grocery stores, church, going out to dinner, driving, et cetera, with the coughing and the fear of coughing. In the past, I was prescribed many different medications which did not give me any relief; therefore, I am not on any medication and I continue to cough every day. My family and I would be ecstatic if I could find any relief to this cough.

In closing, I am grateful to be able to share my journey as a chronic cough patient, and by me sharing what I have endured will help all these other suffers of this debilitating disease with the help of the FDA. If by me sharing my journey and help just one person and their family, it would mean the world

to me. Thank you for your time.

DR. CARVALHO: And thank you for speaking to us.

Next is speaker number 11. I believe speaker number 11 has some slides as well.

MS. SCHROER: Yes.

DR. CARVALHO: Speaker number 11, please unmute and turn on your webcam. Will speaker number 11 begin and introduce yourself? Please state your name and any organization you are representing for the record, and you have three minutes.

MS. SCHROER: My name is Danielle Schroer, and I'd like to discuss the professional and monetary cost of living with chronic cough. I'm in no way being compensated for this appearance. My career is limited to what I can do with this condition, and I'm unable to take any positions that require a lot of talking like interviews or leading meetings because the more I speak, the more I cough. It's one of my triggers. I've had to excuse myself from board meetings because I started coughing uncontrollably, and you can imagine, your face turns bright red. I

start sweating. You're out of breath.

I've seen three allergy doctors; two pulmonologists; a gastroenterologist; my PCP; an acupuncturist; a speech therapist; and have been to the world known clinic. This medication is my final hope to lead a normal life again after 13 years. I have had bilateral steroid injections. I've had Botox injections. I have an umbilical hernia that needs fixed, but there's no sense in getting it fixed. It will just be back until I stop coughing.

I fear that I'm going to cough so hard that I'm going to get a brain aneurysm. Driving can also be scary, as I've had to pull over three times during an event, as all I can see are stars, and lights, and orbs, so I pull over in case I pass out. Then all of this is outside of the normal headaches and exhaustion from the coughs.

As shown in my PowerPoint, at all times I have to have cough drops; Kleenex; cough medicine; Poise Pads; and kids' toothpaste on hand. By the end of the day, every day, my bladder is shot, and that plays a huge role on my behavioral health. I'm

always wondering if my pants are wet, if anyone can see it, and this is why I limit my social groups. I keep it close to friends and family so that way they know my diagnosis.

My cough wakes me up in the middle of the night, at least once, and it's a diagnosis of exclusion, so we spend millions of dollars on doctors and specialists to rule out if it's a certain medication. Is it asthma? Is it GERD? Is it allergies? And if there are no other explanations, then it must be chronic cough. Awareness needs to be brought to this condition, especially due to the excessive burden it places on your daily living and your quality of life, not to mention the amount of time and money it involves.

I provided a short list of my triggers, and this is in no way inclusive. When I shared this information with two of my physicians, they looked at me like I was nuts. Of course, none of it got addressed. As I watch this, I hate to see so many people share my symptoms, but I'm happy that I'm not alone and that someone else is sharing my journey

with me, and to thank all the physicians who are actually taking us serious and will speak on our behalf. Thank you for your time.

DR. CARVALHO: Thank you very much.

The next speaker is speaker number 12. Speaker number 12, please unmute and turn on your webcam. Will speaker number 12 begin and introduce yourself? Please state your name and any organization you are representing for the record, and you have three minutes.

MS. COULOMBE: I'm not representing anybody except myself, and I'm not financially being paid. My name is Susan Coulombe and I'm 74. I've had a chronic cough since my 20s. Living with a chronic cough is very difficult. I've been to many doctors and a voice therapist. Just like everybody else that's spoken, I've had all the tests, et cetera.

Nothing has worked. The doctors don't know how to help me. When I'm around people who don't know me and I have a coughing fit, they stare at me like I have a disease. I have to explain my situation. If I cough hard enough, it can cause me

to vomit. It also causes urine leakage. My husband will turn and stare at me if we're in a room to see if I'm ok. I've tried many over-the-counter medications that haven't worked for me at all. Occasionally, an antihistamine will help stop the post-nasal drip. No sprays have never worked. When I'm in a meeting or movie and have a coughing fit, I sometimes have to leave the room. I get depressed from this condition and sometimes feel hopeless. And again, I'm just hoping for a permanent solution. This just disrupts my sleeping.

I did go to a voice therapist, and the one thing that I came away with that has helped me is she said chew gum when you start having a coughing fit. That has helped. She wrote down that she thought I had laryngeal hyperresponsiveness, irritable larynx syndrome, and vagal neuropathy. Nobody has helped me, nobody knows what to do, and I just pray that somebody comes up with a solution, whether it's drugs, an inhaler, anything to help. This has just really affected my life, and like I said, it causes me depression. Thank you for doing a study, and I

hope it works, and I hope the drug administration allows the medication to come to market. Thank you very much.

DR. CARVALHO: Thank you.

The next speaker is speaker number 13. Speaker number 13, please unmute and turn on your webcam. Will speaker number 13 begin and introduce yourself? Please state your name and any organization you are representing for the record, and you have three minutes.

DR. ZELDES: Good afternoon. I'm Nina Zeldes, a health researcher at Public Citizen's Health Research Group. I have no financial conflicts of interest. Public Citizen opposes FDA approval of gefapixant for the treatment of chronic cough and for adults. The small effects of treatment with the drug do not provide substantial evidence of a clinically meaningful benefit for patients.

We agree with the FDA's assessment of the evidence supporting this application, which is mainly based on the recount of cough data using a proprietary algorithm. Our concerns include the

small treatment difference in cough frequency between groups; the lack of compelling additional data from the secondary endpoints; the large placebo response across all efficacy endpoints; and the potential unblinding of the trials due to taste disturbances.

For example, while there was a small reduction in the frequency of cough of 15 percent in one and 17 percent in the other among patients taking gefapixant compared to those in a placebo group, these results reached statistical significance only in one of the two trials. Moreover, the difference in the proportion of subjects who had a reduction in cough frequency of 50 percent or more was only 6 percent between the two groups. The clinical meaningfulness of these results was further called into question by the FDA's post hoc analysis, which was suggested that compared to placebo, treatment with gefapixant only resulted in a reduction of 1 to 2 coughs per hour.

As highlighted by the FDA, the secondary endpoints did not provide additional support of meaningful benefit for patients and, quote, "must be

interpreted with caution," end quote. For example, different analyses of the data demonstrated that there are generally only small differences between the two groups, and only one patient-reported outcome measure reached statistical significance. Importantly, the FDA found that there was no clear correlation between patients who reported that they were feeling better and those who were coughing less. These small benefits didn't contrast to the disturbances in taste, or loss of taste, that lasted an average of 204 days. They occurred in up to 65 percent of subjects in the treatment group, compared to only 7 percent in the placebo group.

Because gefapixant is being considered for a novel therapeutic indication, there is limited experience in how to best measure and interpret the clinical meaningfulness of treatment effects; however, based on the available data, there is no compelling evidence of meaningful clinical benefit from gefapixant treatment.

If the FDA were to approve gefapixant based on the very weak evidence of effectiveness, it would

also set a concerning precedent for the evaluation of future treatments for chronic cough. Patients with chronic cough deserve an effective treatment. Public Citizen therefore urges the committee to vote no on the voting question and strongly recommends that the FDA not approve gefapixant. Thank you for your time.

DR. CARVALHO: Thank you.

The next speaker is speaker 14. Speaker number 14, please unmute and turn on your webcam. Will speaker number 14 begin and introduce yourself? Please state your name and any organization you are representing for the record, and you have three minutes.

MS. SMITH: Good afternoon. My name is Wendi Smith. I am a 57-year-old, 14-year chronic cough patient, and I have not been paid to make this statement. I don't remember precisely when my coughing started, but my first social media post about it was September 29, 2010. I wrote, "If I cough any harder, my organs are going to pop out." After two years of coughing and many visits to the doctors, with what we thought was a lingering cough,

and trying all of the usual remedies -- cough suppressants, lozenges, gargling throat sprays -- nothing worked. My cough was still there.

I've been coughing so violently that I was dry heaving, wetting myself, and putting so much pressure on my organs that I developed four hernias. Over the next few years, I've had multiple invasive tests; saw pulmonologists; ENT; gastroenterologists; respiratory therapists; a urologist; allergist; and a general surgeon. Nothing abnormal has ever been discovered. I've also tried acupuncture; hypnosis; silent reflux diet; speech therapy; natural remedies; and several medications, including benzonatates; opioids; Trelegy; Nexium; albuterol, Botox injections into my vocal cords; and extremely high doses of amitriptyline and gabapentin.

The physical effects of constant coughing have resulted in four ventral hernias. When I cough, I have to put my hands over the hernias and hold them in to prevent further damage. I also suffer from headaches; pulled muscles; sore ribs; multiple sneezing fits; sleepless nights; and everything that

everyone else has already mentioned.

The emotional toll that this constant coughing has taken on my personal, family, social, and professional life is huge. It's restricted several activities at work. Quality family time is always interrupted. My relationship with my husband is forever changed. If I need to go out, I must make sure I get an aisle seat and know where the exits and bathrooms are so I can escape quickly. Out of town travel, especially on trains or airplanes, presents quite a challenge.

My eldest daughter's wedding is this December 15th, and I am so afraid that I will ruin the ceremony, and I am exhausted. On September 6th of this year, I had a stress-related heart attack; me, vivacious, energetic, healthy me. The examinations revealed no heart or arterial disease, only stress from dealing with this incessant coughing.

The totality of this cough is immense, affecting every aspect of my life. After more than 14 years, I am desperate that something be

discovered, created, or approved so that I can live a more viable and effective life. Thank you for allowing me this opportunity to speak.

DR. CARVALHO: Thank you very much.

Our next speaker is speaker number 15. Please unmute and turn on your webcam. Will speaker number 15 begin and introduce yourself? And please state your name and any organization you are representing for the record, and you have three minutes.

MS. MARKEL: My name is Deb, and I am a patient dealing with a chronic cough. I am not being paid to speak today. I've had a cough for approximately 30 years. After trying numerous ways to alleviate it with my internist for years, I was referred to an allergist -- no allergies found -- and an ENT. I started on a low dose of gabapentin, which helped somewhat, so I accepted that a cough was something I had to live with.

After moving to Florida seven years ago, I again worked with a new internist on ways to alleviate my cough. After trying many things, I went

to a pulmonologist and another ENT with no improvement. I was finally referred to a cough specialist. I've been seeing him and his staff for 11 months with some improvement, but I'm still dealing with coughing episodes. After trying different medications, gabapentin was increased to 600 milligrams a day, which caused brain zaps, a weird tingling feeling that lasted for a brief second. When the dosage was lowered, these went away.

The cough can be triggered by smells, tastes, choking on food, water, but mainly on mucousy saliva that gathers in the back of my throat. A coughing episode can last from 30 seconds to a minute, and includes many hard coughs and several big sneezes with a significant amount of mucus. I have these several times a day with no warning on when they will happen. Additionally, these episodes have caused urinary incontinence.

This cough has affected talking on the phone; public speaking; attending worship services; singing in the choir; leading a small group; and attending

meetings, all of which have had an impact on my life. It has given me a hoarse voice. My family and friends have learned to deal with me excusing myself during dinners and family gatherings. My husband used to be concerned over bad episodes, but now he's numb to the situation. It sometimes interrupts our conversations, which over time has had a negative effect on our relationship.

A friend who I meet with weekly shared these thoughts. "Deb's coughing fits are relentless when they begin. They are so intense, I feel compassion for her. It is hard to listen to, and I know she is frustrated and embarrassed. Deb deserves to have the privilege of being rid of this for the remainder of her days."

This cough has taken away my freedom to live a normal life. My hope is that improvement or even a cure can return me to a place so I can look forward to important events in my life and the lives of loved ones without the fear of embarrassment and disruption. Thank you for allowing me to share my journey.

DR. CARVALHO: Thank you.

The next speaker is speaker number 16. Please unmute and turn on your webcam. Will speaker number 16 begin and introduce yourself? Please state your name and any organization you are representing for the record, and you have three minutes.

MS. MOON: Hi. My name is Karen. I'm a patient. I'd like to state that I've not been paid to speak at this meeting. I've had a chronic cough for almost 20 years. You have heard the same from all the speakers today. How many more out there are living with a chronic cough and hoping for a new option for treatment? I, too, have seen many local doctors over time: primary care; allergists; ENTs; speech therapists; gastroenterologists; chiropractor; and even a hypnotist. Many treatments were tried, and all that have been mentioned, nothing helped. Some doctors thought my cough was emotional and wanted to prescribe meds to calm me.

In 2013, after 10 years of coughing, I went to the Cleveland Clinic in Ohio. Several diagnostic tests were completed and several medications tried.

Also, steroid shots were injected into my superior laryngeal nerve endings twice, and Botox was injected into my vocal cords twice. Nothing worked. The Botox injections caused me to lose my voice for 10 weeks each time and caused painful coughing and difficulty breathing for most of those 10 weeks; however, Cleveland Clinic hasn't given up, as the other doctors did.

I cough many brief and several hard coughs lasting from seconds to about 45 minutes, and I don't mean once, or twice, or five, or ten times a day; I mean constantly throughout a day. My cough has increased over the years and started as a throat clearing, to a quick cough, up to what it is now. Is there a pattern to when or how I cough? I thought about it over the years, but I don't think so. It can come out of nowhere. I cough when I talk, walk, sit, drive a car, when I stand, lay down, when I exercise, brush my teeth, eat, go grocery shopping. You name it, and it's probably when I cough.

I had to retire early from a job I love, school superintendent, because of my cough. It

interfered with meetings and interactions with students, staff, parents, and others. I was an outgoing person before. I loved joining groups, gym, and now I'm not that same person. I've had people refuse to shake my hand, even before COVID, afraid I'd have something contagious. Their reactions are very bothersome, but I do understand.

Coughing is very tiring and can be depressing. I feel alone at times, but I'm very lucky I have a wonderful guy and extended family and friends who stand beside me. Even phone calls with them or anyone are difficult. I'm tired of feeling I have to leave a store or restaurant because I'm coughing so much. I will be 77 in 3 weeks, and it would be great to be relieved of coughing, or at least less coughing, before I leave this world. I don't want to be remembered as the grandma who coughed all the time.

Thank you for allowing me to speak. I hope this information helps the FDA understand the struggles of a chronic cough patient, and in turn can give doctors another option to treat chronic cough

patients so they have better care and a better life. Thank you for listening.

DR. CARVALHO: Thank you.

The next speaker is speaker number 17. Please unmute and turn on your webcam. Speaker number 17, please begin and introduce yourself. Please state your name and any organization you are representing for the record, and you have three minutes.

MR. FERGUSON: Hey. I'm Dave. I've had a chronic cough for about 25 years. I'm a creative director at a company that does work with Merck, which is how I learned of the hearing. But that said, I haven't worked on any accounts related to cough, and I'm not being compensated for sharing my story.

Sometime in my mid 20s I first noticed my cough, and I'm 48 now, so half my life. My cough kind of oscillates between this minor nuisance and extreme disruption. At its worst, it kind of builds through the day and gets worse and worse as the hours go by. By the evening, my head will be pounding from

all the rattling, and I often wonder jokingly if I've ever given myself a minor concussion, but I wonder if there's some truth to that one. I've tried to address this off and on with my doctors over the years, but we've never solved it. I kind of gave up trying at this point. I'm just accepting it.

Cough might seem minor to a lot of folks and temporary, but a way to prevent this really would be nothing less than life changing. When I get home, my 6 year old meets me at the door. She doesn't hear me pull in the driveway, but she does hear me cough when I'm outside. She's worried when I have these coughing fits. She puts her hand on my chest. She tries to calm things down. Sometimes she does these impressions of me, which are a riot, but it'd be really nice if the cough wasn't part of that routine.

Even though much of the world has kind of moved on from the COVID precautions, I'm still a master, and that's really a super understatement because I haven't gone into a public space without an N-95 since February 2020, and the cough is my reason why. It's a big part of it. It's not just because I

want to not get sick or prevent spreading COVID, but it's because when you cough as much, you get super self-conscious, and every single cough, you feel eyes on you.

Sometimes people are glaring. You know people around you are thinking about it and this whole thing. You see other folks around in New York City wearing masks outdoors. There are so many people that have compromised immune systems, and I'm so aware of that. Any cough near them is a potential health risk, so this mask is the only way that I can show that I respect their concerns even though I've got this cough I've had for 25 years. On the train the other day, I had three people that back-to-back left the seat next to me. So if you ever want a row to yourself, just start a coughing fit and throw on a mask, and people stay away from you.

At work, constantly I'm thinking about my colleagues that are sitting next to this non-stop cough, and we joke about it, but it's like who's coughing in the background? Can you mute your mic? This is kind of the common refrain that's just part

of work when I'm at the office. And when I'm home with my family, that's when I'm most aware of it. My wife comes home after a long day, the last thing I want to do is add my jarring cough to her evening. It's not just patients that have to deal with these coughs that won't go away. But the worst thing is, every time my daughter gets sick, I worry that her new cough is the same cough I've had since my 20s. I've had this so long now, I just assume it's kind of with me for life. I can tell you that a chronic cough is not just a huge burden on people like me, but it's also a burden on the people around them.

So I don't know if this stuff you're working on at the moment is going to be the answer for me, but I can absolutely tell you that a remedy would be life-changing. So that's my story, thanks for your time, and thanks for all the work you guys are doing. Hope you're on to something.

DR. CARVALHO: Thank you.

The next speaker is speaker number 18. Please unmute and turn on your webcam. Speaker number 18, please begin and introduce yourself.

State your name and the organization you are representing for the record, and you have three minutes.

MS. ADAMS: Okay. Thank you.

Good afternoon, all. My name is April, and I'm a patient, and I'm not compensated for my time. My cough started approximately 17 years ago. I'm 43 years old. I've seen pulmonologists; allergists; ENT; GI; speech therapist; and endocrinology. My cough can be triggered by anything. I can be sitting, standing, walking. It doesn't matter what I'm doing; it's just triggered at any time.

My cough has limited me to social interaction. I'm isolated. I don't like to travel. If I have to travel, I will have to sit by a window so I can at least turn away, have a mask, and try to contain it as much as possible. If I go into a store, I try to make sure I know what I want, go in-go out, or I'll have to send somebody on my behalf.

It's very frustrating. It's stressful. It seems like no one understands. It was to a point

where I used to carry a doctor's note around. That's how bad it was. I had various testings such as CT sinus scan. I had GIs, chest X-rays, and pulmonary function tests. I've been on various medications. Just to name a few, Trelegy, and I've been on prednisone; HydroMATE; Protonix; Flonase; gabapentin; and amitriptyline. I've been diagnosed with rhinitis; sinusitis; GERD; asthma; COPD; enlarged thyroid; pulmonary nodules; and also vocal dysfunction.

Last but not least, I did go see a cough specialist, and he's been wonderful, about a year ago, and I was finally diagnosed with neurogenic cough. This has been very hard to deal with. I do work for the Department of Veteran Affairs. It was so bad to the point where I asked if I can work permanently from home.

Whatever drugs or whatever you're working on, I pray that it can be some help or give some type of relief because I'm just to the point now that I don't even know if there's anything and just going to be stuck with it until the day I leave. Thank you for

listening, and everyone have a wonderful day.

DR. CARVALHO: Thank you so much.

The last speaker, speaker number 19, please unmute and turn on your webcam. Will speaker number 19 begin and introduce yourself? And please state your name and any organization you are representing for the record, and you have three minutes. Thank you.

MS. KARGER: Hello. My name is Rebecca Karger, and I am a chronic cough patient, and I have not been compensated for any of my comments. I am a retired public health nurse from a small county in Illinois, and I have suffered from chronic cough for about 23 years. Imagine having your nurse having coughing fits while she's treating you. It was very embarrassing for me and very offsetting for my patients, I'm sure.

Over the years, I have seen numerous pulmonologists, all of whom told me that I probably had adult onset asthma. Even all the breathing tests I had did not indicate any form of asthma at all. I was prescribed numerous and very expensive inhalers,

all of which did absolutely nothing, except some of them made me cough even more. Finally, I was referred to Vanderbilt Hospital in Nashville, Tennessee, and that was a good hope of mine, that I would find help. They were no help either.

Sometimes I thought the physicians were thinking that I was exaggerating or even making it up. That was humiliating. I even had a Nissen fundoplication, which eliminated my reflux, but here I am still coughing. I knew I was experiencing real symptoms, and I had suffered much with pain and numerous pulled muscles along the way.

Unfortunately, I found it necessary to do my own research to find a possible answer, and I hoped some relief. After a number of weeks, I found some medical references to something called a chronic cough of neurogenic origin. The description sounded just like me, but now I had to find a doctor who knew about it and could treat it; again, more research. I finally found a physician who not only knew what it was, but specialized in it, so I wasted no time making an appointment, even though I would have to

travel two states away from my home.

Since that time, I have been treated with existing drugs, mostly gabapentin and amitriptyline, which have given me some relief, but I also suffer from the side effects of these drugs, which unfortunately includes weight gain and finding the right combination of dosages: up, down, in between, you never know.

Those of us with this condition need a medication to treat chronic cough without dealing with the side effects of several different drugs combined and always trying to find a therapeutic dosage. I certainly hope that we can find some relief soon, and I really honestly did not know that there were so many people suffering the same way I am, so I'm very grateful to have been here today and heard their stories also. Thank you for letting me speak.

Clarifying Questions (continued)

DR. CARVALHO: Thank you very much, and that concludes the open public forum.

We do not have additional questions at this

point, but we do have a couple of issues that we were still discussing, and I wondered if Drs. Coon and Kelso would like to go back to some of the follow-up questions that they had because the sponsor's now ready with slides.

DR. BOLLINGER: We do have the slides available.

DR. CARVALHO: Drs. Coon and Kelso, would you like those brought up for discussion?

DR. COON: This is Cheryl Coon. I would love to see those slides if we have time for them. Thank you.

DR. CARVALHO: Thank you.

DR. BOLLINGER: Allison Martin Nguyen?

MS. NGUYEN: Thank you. Just to remind the committee, what Dr. Coon had requested were the cumulative distribution curves for the change in cough frequency by PGIC. Slide up. Shown here are the different categories of the PGIC by the percent reduction in 24-hour cough frequency, where we can see that the PGIC does distinguish between the degree of change in cough frequency.

The second was the cumulative distribution curves of the change in cough frequency by treatment group. Slide up, please. Again, here are those curves showing in the blue line, the MK 45-milligram group -- sorry, we have it there, the MK number -- the gefapixant 45-milligram group, and then in red, the placebo. And as we've noted before, there is a change across a range of percent change in cough frequency where gefapixant does show significant benefit over placebo. Thank you.

And I wanted to turn it over to Dr. Berry, who will respond to the comment from Dr. Kelso.

DR. BERRY: Hello. Scott Berry, statistical scientist, consultant to the sponsor, but no other financial interest in the outcome. Slide up, please.

Dr. Kelso asked about a comparison of those with taste AE in the two different treatment arms. We showed this on two different slides, but this slide shows them next to each other. On the left side of this, this shows the population that had a taste AE in each of the treatment arms, so everybody on the left had a taste AE. Those on the placebo

group saw a 47 percent reduction in cough. Those in gefapixant saw a 64 percent reduction in cough, with the constant of all of those patients having taste AEs for that comparison.

So for that group, if taste AEs were driving different responses, those would look similar. Gefapixant has more taste AEs, but that group stratified by taste AEs would look similar, but you see a large treatment benefit for those patients with taste AEs. Thank you.

DR. CARVALHO: Thank you very much.

We're at the section now that we've got the charge to the committee, and we'll now proceed with the charge to the committee from Dr. Stacy Chin.

DR. STEVENSON: Excuse me. Hello. This is Takyiah speaking. Dr. Carvalho, I see that the FDA has their hand raised.

DR. CARVALHO: Oh, ok. Then we'll pause, and we'll have the FDA make their comment or ask their question.

DR. GARRARD: Hi. This is Dr. Lili Garrard, statistician from FDA. I would like to make some

comments based on the data presented by the applicant just now, the percent change from baseline in the cough frequency.

Also, to help answer Dr. Coon's question, first of all, we consider comparing treatments using percent change from baseline has undesirable statistical properties, so including sensitivity to influence the magnitude of baseline value, which is undesirable for clinical interpretation reasons also. For this reason, we consider the absolute change in cough frequency as a better way to look at the cough frequency data.

If we could please bring backup slide number 99 in the FDA's deck. This is also included as figure 5 in the FDA background document. If we look at this ECDF plot, we can say that the cumulative distribution function curves display this continuous view of the change in 24-hour cough frequency from baseline on the X-axis and the cumulative percent of patients reporting up to that level of change at week 24 or week 12 on the Y-axis. So looking at these curves, there is overlapping

curves that we can observe and minimum separation between them.

In addition, just a comment on the applicant's way of looking at the ECDF curves by the PGIC response categories, one important consideration is that it is not appropriate to just focus on one point estimate, which was done by the applicant, just looking at the mean change in the minimally improved category. It is important to look at the entire distribution of all the response categories and also maintain a balance of trying to maximize the amount of patients, the number of patients, who truly experience a meaningful change compared to those who did not experience a meaningful change; for example, no change or worsening.

In addition, FDA has been clear in our guidance for years that it is important to triangulate information from multiple anchors so that we can derive a plausible range of changes that may be considered meaningful to patients, and this also needs to take into consideration the patient's baseline status.

So with that, I hope to clarify some of the questions that the committee may have. Thank you.

DR. CARVALHO: Thank you for those comments.

So now, we'll proceed to the charge to the committee and Dr. Stacy Chin.

Charge to the Committee - Stacy Chin

DR. CHIN: Good afternoon. I want to thank the patients who provided their perspectives during the open public hearing today. I will now provide the charge to the committee.

As you have heard, gefapixant is a new molecular entity proposed for the treatment of refractory or unexplained chronic cough, which is a common symptomatic condition with no approved therapies. This is a novel indication with no precedent for optimal study design or efficacy endpoints.

Gefapixant is the first application to be reviewed by the FDA for this indication. As such, there's no prior experience with a clinical interpretation of results for these efficacy endpoints; however, given stakeholder interest in

this therapeutic area, your input is quite valuable not only for the application before us, but also for informing the guidance we will provide to other development programs moving forward.

As a reminder, the key findings observed in the pivotal trials were: a wide variability in the baseline cough; a high placebo response across endpoints. This led to a small reduction in the primary endpoint of cough frequency relative to placebo with statistically significant results in one of the two trials. There was a small effect on some PRO endpoints and the safety profile is notable for frequent reversible disturbances in taste.

We acknowledge that in the absence of approved therapies, one might say that any improvement in cough is automatically meaningful; however, we must balance speeding patient access to new therapies with having reasonable certainty about a drug's benefit. As noted in the FDA presentations, there are numerous issues and uncertainties that make it challenging to interpret the results and difficult to definitively conclude that the results are

clinically meaningful, particularly when patients experienced similar improvements, whether they received placebo or gefapixant.

As mentioned in the opening remarks, in the benefit-risk framework, the benefit must be clinically meaningful to outweigh both the risks and uncertainties in order to conclude that the benefit-risk assessment is favorable on a patient population level. If there is not a clinically meaningful benefit, the product only confers risks no matter how mild those risks might be. It is for this reason that the main question before the committee is whether gefapixant has demonstrated a compelling clinically meaningful benefit over placebo for the treatment of refractory or unexplained chronic cough.

I will now turn to the discussion points and voting question. Discussion point 1. Discuss the evidence of effectiveness for gefapixant for the treatment of refractory or unexplained chronic cough in adults. Specifically address the following: the small reduction in cough frequency compared to placebo and the clinical meaningfulness of the

reduction in cough frequency; the observed results from PROs and whether these results provide compelling evidence to inform the clinical meaningfulness of the reduction in cough frequency; potential unblinding of patients due to taste disturbance and its impact on interpretation of cough frequency and PRO results.

The second discussion point, we'd like you to discuss the overall benefit-risk assessment of gefapixant for the treatment of adults with refractory or unexplained chronic cough, a symptomatic condition.

Our final and only voting question, we'd like you to determine whether the evidence demonstrates that gefapixant provides a clinically meaningful benefit to adult patients with refractory or unexplained chronic cough, given the small reduction in cough frequency and results from PROs. We ask that you provide a rationale for your vote. If you conclude that there is insufficient evidence of a clinically meaningful benefit, please describe the evidence that could be collected to show a benefit

that is clinically meaningful.

I will now turn the meeting back over to the chair, Dr. Carvalho.

Questions to the Committee and Discussion

DR. CARVALHO: Thank you, Dr. Chin, and the committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, the public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording, then we will open the question for discussion.

Discussion point number 1, for question 1, discuss the evidence of effectiveness for gefapixant for the treatment of refractory or unexplained chronic cough in adults. Specifically address the following: A) the small reduction in cough frequency compared to placebo and the clinical meaningfulness

of the reduction in cough frequency; B) the observed results from patient-reported outcomes, PROs, and whether these results provide compelling evidence to inform the clinical meaningfulness of the reduction in cough frequency; C) potential unblinding of patients due to taste disturbance and its impact on interpretation of cough frequency and PRO results.

Are there any questions about the wording of the question?

(No response.)

DR. CARVALHO: Seeing none, if there are no further questions or comments concerning the wording of the question, we will now open the question for discussion.

Dr. Kelso?

DR. KELSO: I think that the analysis of looking at this in mean or median coughs per hour and the absolute reduction in that is the easiest to grasp, and perhaps the most clinically relevant. So if we look at the data that says instead of coughing on average 20 times per hour, 18 or 19 times per hour, if that seems not meaningful or not relevant,

and then you say, well, there's a broad range in that, and people have coughing spasms, and there are other ways; and even though it's a tiny absolute difference in certain patients, it might be of more consequence, so the other way is to ask the patients.

But if you look at the data on the PGIC, where they're asked if their cough is a little better, a lot better, et cetera, that just absolutely does not pass the eyeball test. There's just no difference in patients' perception, if their cough -- however they want to decide that. It's up to the patient to incorporate all those other factors and say if their cough is better or not, and there's just absolutely no difference in the percentage of patients who said their cough was a little better or a lot better relative to whether they were getting the placebo or either dose of the medication.

So the fact that only one of the two studies showed a statistically significant achievement of the prespecified endpoint already makes it a little suspect, and then the tiny absolute difference with the drug and the apparent no difference to the

perception of the patients about whether or not it was effective, I think it's pretty clear, to me anyway, that this has not shown any perceivable effectiveness.

DR. CARVALHO: Thank you, Dr. Kelso.

And now, Dr. Hunsberger?

DR. HUNSBERGER: Yes. Sally Hunsberger. I found the public speakers very, very helpful while thinking about this because what I heard them stressing was that it was the episodes and the clusters of coughing that was really affecting their lives. So this endpoint doesn't seem to capture any reduction in episodes. I think the number that they're looking at isn't really a good measure of that.

I don't know the method that they are using to collect this data, if it's at all possible to look at clusters, and is there a reduction in clusters. But my concern, if this was approved, is that would kind of establish these endpoints as the ones that future research would be allowed to look at, and I still don't think we've quite captured what the good

endpoint is because, clearly, there really is a minimal effect going on. So my concern is just that we don't really have the right endpoint to establish whether this is a beneficial drug or not. Thank you.

DR. CARVALHO: Thank you.

Dr. Coon?

DR. COON: Hi. It's Cheryl Coon. I appreciate the last panelist's very pragmatic approach to discussing the endpoints. At the risk of getting a little bit into the weeds, I wanted to provide the perspective of somebody who develops and interprets COAs for my day job.

Regarding the first, the primary endpoint of cough frequency, it does seem like it is a relative concept to people experiencing chronic cough, at least according to the literature, with qualitative studies that have been done, including those that have been done by the sponsor, and it does seem like the sponsor did their job in terms of validating the recount approach that was requested.

Although the primary cough frequency endpoint did reach statistical significance in one of the two

studies, the empirical cumulative distribution functions for the raw change in the 24-hour cough frequency that I saw, they barely separate between placebo and gefapixant. When the raw change was converted to percent change, the group separates more, but the separation is consistently small, and the use of percent change certainly has its own interpretation issues because it becomes a different number, depending on where you are at baseline.

So setting aside the fact that there are some questions about how much change would be meaningful, even if we don't have the confidence in that, there isn't actually a place on the cough frequency scale where the groups separate enough to be able to say it would be meaningful.

Just to the point about -- I think it was the secondary endpoint that was alpha controlled for the 30 percent reduction in cough frequency, that 30 percent reduction was based on a minimal change on the PGIC anchor, so I would not consider that an appropriate endpoint. It would have been better if it had been increased to 50 or 70 percent, based on

the PGIC anchoring work that was done. I certainly agree with the agency that more anchors and more analysis methods are really needed to gain confidence in terms of where that threshold gets set.

I also do want to speak to the secondary endpoints, the other PROs.

Dr. Carvalho, is that the B part of this question? Can we speak to that now or do you want to do it separately?

DR. CARVALHO: I think you can go ahead.

DR. COON: Okay. Thank you. The concepts of physical symptoms, social impacts, and psychological impacts that are included in the Leicester Cough Questionnaire certainly do appear to be relevant according to the people experiencing chronic cough, and we heard much of that today. But the concern was with the use of the LCQ total score as an alpha-controlled secondary endpoint because social and psychological impacts that are components of that total score, they can actually be impacted by things beyond the medication that's actually being evaluated here. So while those data are certainly relevant for

evaluating the efficacy overall and painting that picture, having those rolled into secondary endpoints seems inappropriate and out of order. Perhaps that should have been secondary endpoint, whereas the physical symptoms score would have been better to be an alpha-controlled secondary.

Further, the responder definition that was used for the LCQ total score, that was discussed at length today, and from my judgment, it was indeed set too low at 1.3 because it was based on the minimal improvement group on that PGIC anchor. So it would have been preferable if that responder endpoint that was again alpha controlled would have used a higher threshold.

My judgment of that endpoint, even though it did reach significance, it was not something that we should be able to rely upon. Instead, we need to look at the supplementary PRO analyses for the exploratory endpoints and, again, they can certainly be used to paint that picture of what's happening from the patient's perspective, which is really ultimately what we're trying to do here.

If we consider the LCQ total score, because that was what much of the data were presented on, thinking about it as kind of the total overall patient experience, if we use those higher responder threshold locations, there does seem to be some separation between treatment arms in P030 but not necessarily in P027.

For the Cough Severity Diary, which didn't have much discussion today -- likely because it was an exploratory non-alpha-controlled endpoint -- it does seem to be like it was well developed. They worked with patients to develop it and have psychometric evidence to support it, but it shows modest separation between those treatment arms at the threshold of 2.7, which is the one that I would judge to be the appropriate one, given the data at hand.

Then the final PRO in the endpoint hierarchy was Cough Severity Visual Analog Scale, and that scale itself raises some concerns because of the use of a visual analog scale. It's often discouraged because they can be difficult to reliably interpret or to use, especially ones like this one, without

anchors along the scale.

So looking at the entire body of PRO evidence from these studies, the supplementary PRO information is generally consistent with that trend of a very small benefit with gefapixant beyond placebo, but I don't see convincing evidence, however, that these small benefits would be considered meaningful. Thank you.

DR. CARVALHO: Thank you, Dr. Coon.

Dr. Evans?

DR. EVANS: Hi. This is Scott Evans from MD Anderson, Houston. A lot of the things I was going to say have been said over the course of the last few commenters. I share the concern about the small effect size, and especially the lack of correlation between reduction and cough frequency and the PROs.

That said, I also anticipate that there is enough heterogeneity between the patients in this population. The groups were balanced it seems, but there's a very wide range of cough frequency within each group, so much so that I anticipate that

detecting a statistically significant difference, at least in the one trial, is likely to reflect a real and genuine difference.

I, unfortunately, do not in any way anticipate that this agent will have the kind of clinical effects that were hoped for by the individuals who were presenting in the open public hearing, who were hoping for elimination of their cough, but on balance, I do think it's likely that we could expect at least a modest effect in patients on this agent, and I'll stop there. Thanks.

DR. CARVALHO: Thank you.

And Dr. Kim?

DR. E. KIM: Edwin Kim, University of North Carolina. First of all, I will say that the testimonials shared by the sponsor, as well as the actual patients themselves are quite compelling. I've also seen these patients in my own clinic, and I think there's no doubt that there is a need for a treatment for patients with chronic cough, as has been described.

For this particular case, I go back to what

the sponsor shared as far as the mechanism of the medication itself. It seems that it is able to stop the actual cough itself by the ATP cough signal, thereby reducing the frequency of the cough. So again, we have this gigantic placebo effect here that's not that, so the sponsor shows a small improvement compared to placebo, which in my mind is the drug effect; so not the 60 percent, but the difference there might be the drug effect, at least it seems that way to me.

But giving them the benefit of the doubt that there is this drug effect, again, going back to those compelling stories, many of these stories are discussing disturbances with their daily activities, and life, and these other factors, and I would like to think that the way that the drug works, decreasing the frequency of cough, should correlate with those. So to not see that correlation is worrisome to me that the medication, at least the way it's supposed to be working, is not effective in actually improving those PROs. So any improvement seen may be coming from some other factors other than the medication

itself, so just some of the concerns that I have.

Then the potential unblinding, the taste disturbance there, again, when there's such a small effect, as the FDA said, it's not that it's necessarily unblinded, but it just creates some uncertainty around it. And if there were a large treatment effect, I think that might be easier to let go, but when the treatment effect seems to be on the smaller side, I think any uncertainty is noteworthy. Thank you.

DR. CARVALHO: Thank you, Dr. Kim.

Dr. Hamblett?

DR. HAMBLETT: Thank you. Yes. In terms of the cough frequency data and the original primary analysis, I did find it striking that the confidence interval for that estimate, particularly for the 24-week trial, actually excluded the effect size that was seen in the phase 2 study, so that to me was important. Again, that doesn't mean that there's not effect there, but it was meaningful to me that there was sort of an upper bound on that efficacy effect.

And I agree with Dr. Hunsberger's comments

about finding the right endpoint; to me, not even just the PRO data, but another objective measure. I heard a lot in the public comment about incontinence, and I know there was another study that we're not reviewing today, but the potential to refine endpoints along that line would also be very, very helpful in this setting to more directly capture those events that seem to be most meaningful to how patients feel, function, and survive.

DR. CARVALHO: Thank you.

And a comment from the sponsor? We have Merck, Alysia Halsing [ph].

DR. BOLLINGER: Yes. We're going to have Dr. Philip come to the microphone to share some data on different thresholds. Thank you.

DR. PHILIP: Thank you. George Philip, medical affairs. We've heard interest in different levels of defining a responder, in addition to the 30 percent reduction from baseline and cough frequency, to also see what it may have looked like or what it did look like at 50 percent reduction and 70 percent reduction, as other thresholds to define a

responder. We have performed those analyses, which I'd like to share with you now when the slide is available.

What you will see when the slide comes up is that by setting a more rigorous level of response required, we see relatively less placebo response and relatively more active response in relation to the placebo response. Slide up. When the slide is available, you'll see the pooled analysis on the primary endpoint at week 12 at the 30 percent, followed by 50 percent and 70 percent reductions.

If we can see the slide.

DR. STEVENSON: Hello. This is Takyiah speaking, the DFO.

Dr. Carvalho, I just wanted to make sure that the sponsor is permitted to show their slides. This is the committee discussion, so I just want to make sure that it's ok with the committee, with you, Dr. Carvalho, for the sponsor to show their slide.

DR. CARVALHO: Yes. Let's go ahead and see this slide because it directly affects the questions being asked.

DR. PHILIP: Thank you.

When we bring the slide up, you'll see placebo and gefapixant bars at each level of threshold to define a responder. You'll see gefapixant is consistently higher than placebo at each level, but at the bottom of the slide, you'll see the odds ratios in addition to the estimated differences between those proportions of responders. With the higher levels of defining a responder, we see greater odds ratios associated with the more rigorous definition, and all three of these cutpoints support the benefit of gefapixant over placebo in cough frequency reduction at different levels that are each meaningful for what patients can perceive as an improvement from baseline. Thank you.

DR. CARVALHO: Thank you.

Dr. Courey?

DR. COUREY: Thank you. I really appreciate seeing that last slide, particularly on the changes of the separations of the groups with higher frequency of reduction. It was very interesting. However though, the small reduction in cough

frequency is very concerning, especially because the majority of patients can tell when they're on medication. PROs are all very subjective, and they are influenced by the day the patient takes them, the situation in which the patient takes them, and then we always talk about their subdomains. And what we saw here is that the subdomains all varied very much together, really meaning they're measuring the same thing, not something different as intended.

So the fact that the taste disturbance was so present and two-thirds of the patients when you have a minimal response, and much of that is judged on PRO, it's very concerning to me. So I think that states what I feel on the question. Thank you.

DR. CARVALHO: And the FDA has a comment.

DR. GARRARD: Hi. This is Dr. Lili Garrard, statistician from the FDA. I need to make a comment, a couple comments, regarding the applicant's exploratory responder analysis that they just showed.

First of all, we know that the exploratory analysis was based on pooled data from P037 and P027. We have made it very clear in our backgrounder that

we need to review each investigation on its own merits. And second of all, regarding responder thresholds, those should not be based on arbitrary selection. Those responder thresholds need to be prespecified and with sufficient justification that the selected thresholds represent clinically and meaningful change from the patient's perspective. So I would interpret those exploratory analyses with extreme caution. Thank you.

DR. CARVALHO: Thank you.

Next is Dr. Schwartzott.

MS. SCHWARTZOTT: I am your patient representative, so I have a different viewpoint than most doctors would have. As someone who's lived with a chronic cough for a very long time, I understand the need that these patients have. What you consider a small reduction to us might be extended quality of life and be meaningful enough for us that we would take the risk. Simple treatments can make a difference in our quality of life, whether that be the social, the physical, work related, home related, because everything is affected by a chronic cough.

Any improvement is something to a patient that has a severe cough.

Of course we want better results. We want something that lasts longer. We want something that totally stops it, but this is a start. So the fact that there are so few adverse events, I'm leaning towards questioning if this is the way we should go because if it doesn't work, they can stop taking it. There are adverse events. I've had taste disturbances, severe taste disturbances, and they are brutal. But if the taste disturbance is only minor, then, to me, the reduction in cough, even if it's a small one, might be worth it.

So if the patient takes the medication and it works for them, that's wonderful. If they take the medication and it doesn't work, they can just stop it. If they take the medication and get those adverse events, they could decide whether or not it's worth it to them. But the fact that there's no major safety issues, a patient is going to be more inclined to go with something that may not be perfect, but at least to something in the short term. And hopefully

companies like this can continue to work and develop more treatments that do have more data and do have more treatments, but this is a start.

So I want to make sure that when you're looking at all the data, which some of it I understand and some of it is a bit confusing, the fact that there are few safety issues leads me towards really questioning or thinking we should move forward with this. I mean -- let's see. I've lost my train of thought. Sorry. That's the way I'm feeling towards this, so keep in mind the patient outcomes for sure.

DR. CARVALHO: Thank you.

Are there any additional comments from the panel? Emma D'Agostino?

DR. D'AGOSTINO: Thank you. Just one final thought on the endpoint. I agree the reductions in frequency are small, and point absolutely taken from our patient representative as well. I had the same thought as we were listening to all of our public speakers, that the endpoint really doesn't seem to exactly capture what the patient seemed to be

experiencing.

I would love to hear, if possible, from the sponsor or the FDA on whether it is possible at all to capture from the existing data, and whether the recordings that we have from this trial actually do see that the coughs are happening in fits and whether there is a new way that we could analyze that data, or whether there has been an analysis on whether there's a reduction in coughing fits or bouts of coughing because that seems to be very important to the patients. Then if it's not possible for this trial, I think that's something, as others have noted, that would be very important for future trials. But I absolutely agree that if the coughs are happening in a more steady cadence, that 1 to 2 coughs an hour does not seem particularly meaningful to me, and the lack of correlation to PROs is also concerning.

DR. CARVALHO: Thank you.

Dr. Courey?

DR. COUREY: As an otolaryngologist who sees 3 to 5 patients with chronic refractory cough per

week in my office, I really very much appreciate Dr. Schwartzott's experience and opinion. Cough as the behavior, if it's non-productive, can be suppressed. So the fact that the patients could know when they were on medication would allow them to change their behavior to even suppress the number of coughs, and that's our primary mode of treatment right now for these patients, is to change their behavior in response to the sensation. So now that they have the sensation that they're on the medication, they can reduce their cough frequency while they're awake, and that's another reason the data doesn't correlate with the PROs, because the patients want to get better.

Then the unintended harm from this, or consequences, that every patient with a chronic cough goes to their PMD and they get this medication, and then we know it takes 24 weeks to know if you're going to really respond, even though you can see by 4 weeks they're going to respond or not, the patients are stuck on the medication for 24 weeks. I'm very concerned about the unintended harm that could happen

from that sort of an approach.

DR. CARVALHO: Are there any additional questions?

DR. BOLLINGER: We would really like the opportunity to comment.

DR. CARVALHO: Granted.

DR. BOLLINGER: Thank you.

Dr. Smith?

DR. SMITH: Thank you, Dr. Bollinger. There are a number of things I would like to comment on, and then I'll perhaps work backwards. First of all, if you look at the graphs on the cough frequency and the patient-reported outcomes, nobody had to wait 24 weeks to respond. These patients got most of the efficacy at just 4 weeks. In some of the phase 2 trials, we saw efficacy after just 4 days, so there is not a long wait.

Also, I'm hearing repeatedly it's sad that the PROs do not correlate with the cough frequency. That is absolutely true. If you try and correlate the PROs with absolute changes in cough, patients do not appreciate absolute changes in cough. It is not

relevant to them, so of course it doesn't correlate. But the sponsor's data shows that the minute you try and correlate those things with percentage change -- so the relative change from the patient's baseline -- you see correlation coefficients of greater than 0.6. So I just don't think the data suggests that that's the case.

Then the third and, I think, final thing I'd like to comment on is this question about cough bouts and clusters of coughing. We can absolutely appreciate the way coughs cluster in these sound recordings. The difficulty that we have is there is no agreed definition of a cough cluster or how you decide where a cluster starts and finishes. That's a substantial piece of work in itself to derive an endpoint. It's something in my own academic group we've been looking at. There are many different ways of approaching it, and the work we've done so far looking at different ways of clustering coughs and correlating them with patient-reported outcomes, we're struggling to find definitions that perform better and will correlate better with PROs than the

simple cough frequency. And I'll finish by saying, as I said already, the simple cough frequency and its change relative to baseline does correlate with the PROs. Thank you.

DR. CARVALHO: Thank you very much.

Dr. Kelso?

DR. BIRRING: Can I make a further comment? It's Surinder Birring.

DR. CARVALHO: Is the FDA ok with industry making a comment at this point?

DR. CHIN: Stacy Chin, FDA. As long as it's pertinent to answering one of the questions that the committee has posed.

DR. BIRRING: Thank you. I just wanted to further elaborate on the discussion around the correlation between objective cough frequency and PROs and patients' perception. Slide up, please.

This is data from one of the gefapixant trials, correlating 24-hour cough frequency and a range of PROs. At the top is LCQ, the total score and all its domains, and then some of the other secondary endpoints, CSD and VAS. And as you can

see, there was a moderate correlation between the two, as we would expect, because cough frequency is just one domain, as we've just heard from listening to our patients, but they also suffer from intensity and impact, and the broader impacts of cough, which is captured by the PROs, but there is this association.

We could further look at this association in another way -- slide up, please -- by looking at the different categories at baseline for the LCQ score. The first column on the left is severe health status impairment as measured by the LCQ, and what we see is a stepwise progression in cough frequency scores.

Then one final point -- slide up, please -- is there were greater improvements in LCQ total scores among cough frequency responders, so if I may take you through this slide, on the left is the change in LCQ score, and this is pooled data from phase 2. We have three categories of cough frequency responders and a 30 percent threshold, a much larger 50 percent threshold, and a massive 70 percent reduction threshold.

The first point to make is the LCQ improvement was much higher in those responding with a cough frequency response versus those who did not have a cough frequency response, as we can see on the left. But then we look across this chart, and the more the cough frequency, the greater the patient perceived improvements in their cough. So I would suggest there is a very good link between objective cough frequency measures and patient perception that support the efficacy of gefapixant when compared to placebo.

DR. CARVALHO: Thank you, and I'm going to call on the FDA next for comment.

DR. BEAN: Hi. Thank you. This is Rachel Bean, clinical reviewer. I just wanted to make sure that everyone recognizes the analyses that are being shown about the correlation by the sponsor, they are based on the phase 2 study, P012. So the cough frequency data that was used that resulted from those studies was not captured by the validated cough counting method, so we have not reviewed these correlations, and they're considered exploratory as

well.

So I think more central to the question that we're looking for the committee to discuss would be the pivotal trial data based on the validated cough counts and, again, coming back to what can we make of that data, as it can inform whether there's a clinically meaningful benefit in these trials. Thank you.

DR. CARVALHO: Thank you very much, FDA.

In the interest of time, we're going to go to Dr. Kelso, and then we'll summarize.

DR. KELSO: Can you tell from the recording device when the patient is asleep? And if so, do we have data on cough frequency during sleep or at least during sleep hours?

DR. BOLLINGER: Would you like us to respond to that, Dr. Carvalho?

DR. CARVALHO: FDA, do we have time?

DR. CHIN: Yes. We could also respond to the question, if needed. It needs to be quick.

DR. BOLLINGER: Alright.

Dr. Smith?

DR. SMITH: Thank you, Dr. Bollinger. So you can estimate from the recordings when the patients go to sleep. It's a 24-hour recording of somebody's life. You can't be absolutely certain. It's not the same as a sleep study.

What you see is that there's a great deal less coughing with patients during the night, and the coughing appears to tend to occur during more wakeful periods, which has been corroborated in a much older study in a different patient group, that these small amounts of coughing occur during periods of arousal. So the result of that is you see few amounts of coughing. It's very variable, so it has very little power to detect differences, unlike coughing during waking periods. Thank you.

DR. CARVALHO: Thank you very much.

So let's go ahead and try to do a summary of what we've just been discussing. I think everybody agrees that that this is a huge unmet need, and everybody understands the complete discomfort that these patients have and how this can be so detrimental and life-changing for them.

Again, we're in a little bit of uncharted territory because we don't have prior experience with the interpretation of these kinds of results. We don't have a good precedent for endpoints, and we are hearing loud and clear that endpoints do need to be rethought and reconsidered. There is concern about the small impact on the cough reduction, and there's been quite a bit of discussion back and forth about the PROs and the cough reduction, but that is an issue. Again, finding the right endpoint does need to be reconsidered. There's a very small absolute difference in the mean and median coughs per hour. Asking patients, of course, we want to ask patients. We want to get the patients' feedback on how they feel and try to corroborate it with standard evidence that is tight.

There's been discussion about how to count these coughs, should we do the clusters, and we've had some discussion just recently on how these can be done: clusters, periods, versus individual coughs or coughs that are more widely spaced; coughs that occur at different times of the day or night.

The PGIC anchoring work, where we looked at the data at 30, 50, and 70 percent, probably does need a little bit more explanation. Again, we don't really know how to assess meaningfulness when we have this placebo response that essentially mirrored in the studies, in the graphs, the effects of placebo versus gefapixant. The LCQ of 1.3 was thought to be set too low. Perhaps a higher threshold could be considered. The Cough Severity Analog Scale may be unreliable, and again, because there are no anchors along the scale, getting something else that has better anchoring to be able to pinpoint effects a little bit tighter would be beneficial.

Again, a lot of the panelists did reiterate a lot of the points that were the same: small effect size; reduction in cough frequency; the PROs and the discordance between them; and a modest effect only. But again, there is discomfort with the lack of correlation with the effect and with the PROs, and then the uncertainty, when we're looking at question 1, part C, and the uncertainty about the effect about the taste alteration.

So that is kind of a nutshell of the discussion here for question 1. Shall we go ahead and -- it's about time or a couple minutes for a break, if that is ok.

Takyiah, you can confirm if it's a good time for a break at this point, which is on the schedule.

DR. STEVENSON: Hi, Dr. Carvalho. This is Takyiah speaking. Yes, it is a good time for a break. Thank you.

DR. CARVALHO: We can take a quick 10-minute break. Panel members, please remember that there should be no discussion of the meeting topics to other panel members during the break, and we'll reconvene in 10 minutes, at 3:40 Eastern Time.

(Whereupon, at 3:28 p.m., a recess was taken, and meeting resumed at 3:39 p.m.)

DR. CARVALHO: Okay. Thank you, everybody, and welcome back from a short break.

We now have question 2 of 3, and the question is a discussion question, and it reads as follows. Discuss the overall benefit-risk assessment of gefapixant for the treatment of adults with

refractory or unexplained chronic cough, a symptomatic condition. So we'll open this up to the panel for discussion.

Dr. Hamblett?

DR. HAMBLETT: Yes. I had a clarifying question just about the question itself for Dr. Chin. In the charge to the committee, I believe there is a slide about discussing the benefit versus the risk and uncertainty of the drug. So I just wanted to clarify that this question is focused more specifically on benefit versus risk. Thanks.

DR. CHIN: Hi. This is Stacy Chin, FDA. It is more focused on the clinically meaningful benefit; however, we do have a question focused solely on clinically meaningfulness, so I think you can consider the risks and uncertainties in this question and your discussion of it, because I think the uncertainties about the treatment benefit certainly factor in.

Does that answer your question?

DR. HAMBLETT: Yes. Thank you.

DR. CARVALHO: Thank you.

Dr. Bacharier?

DR. BACHARIER: Yes. Thanks. So I find it interesting that in the wording of the question there's the qualifier, a symptomatic condition, and I think that's probably intended to remind us that this is not a directly life-threatening condition, but I hope it doesn't in any way lead to a trivialization of the severity of the syndrome that we're discussing because I think we've been very clearly informed, and we've had many folks highlight the true burden of disease that this offers.

But as I think about the concept of benefit to risk, the risk I assess is really pretty low. The taste disturbances are probably tolerable to the vast majority of patients who find their cough intolerable. Maybe it's trading one small issue for a much larger life-compromising issue. I think we saw in the data presented that there was a percentage of folks who discontinued the medication because of it, but the vast majority of folks with reported disturbance soldiered through that effect, presumably because of a perceived benefit.

So the risk side of it I think is actually quite low. The uncertainty, if we add uncertainty to risk, it ups the denominator element. But I think that's a really important factor to keep in mind as we weigh whether the magnitude of benefit is meaningful enough to offset what little patient-level risk there is. There's interpretive risk, but I don't know that that's the risk that's really being highlighted here. So I think it's really important we try to balance these as we work through it. So I'll stop there. Thank you.

DR. CARVALHO: Thank you.

Dr. Kim?

DR. E. KIM: Edwin Kim, University of North Carolina. So speaking to this question, like Dr. Bacharier just mentioned, I think the personal risk of this taste disturbance that's been reported, as well as some of the other AEs that were in the slides, I would agree. I mean, everything seemed to be reported as mostly mild, maybe some moderate, so the personal risk seems to be low. Again, trying to think about it as a risk to benefit, we've already

discussed in the previous question the benefit that's there, that there seem to be a benefit, again questionable about how big of a benefit.

I did want to take a second here just to bring up, though -- again, I come back to this idea of these testimonials and how difficult it is to live with this 10-plus years of disease for some, maybe even 30-40 years. Assuming many entered this trial looking for help, and then having a 28 percent dropout rate, suggests there's something maybe off with this benefit-risk ratio if up to almost a third of these patients don't stay on.

Dr. Bacharier mentioned the term "soldiering on," which, again, if there were a stronger benefit-to-risk ratio, I would hope or I would expect to see a higher number there, and then, again, 14 percent of patients dropping out specifically from this taste side effect. This is a chronic disease. This is not curative in any way that I think has been described to us, so it would be anticipated patients would stay on this for quite a while. So this risk-benefit ratio, we're assessing it all for a

shorter amount of time for the trial, but I think it might be important for us to also be thinking about it in a slightly longer term. Thank you.

DR. CARVALHO: Thank you, Dr. Kim.

Any other comments from the panel? Dr. Rank?

DR. RANK: I'm thinking about it similarly to the way Dr. Kim is thinking about it, the small but uncertain benefit balanced with a probably mild-to-moderate side effect that seems reversible about everybody. If we think about the average person who would enter the study that has a terrible cough, the people we've heard from would most likely be experiencing the benefit placebo. The placebo group had a huge response, and there's a small response relative to that placebo group. Of those people who are receiving that benefit directly from the drug as opposed to the placebo, there's a large number of people who are potentially having a placebo effect or having this adverse effect, and I think that speaks to the importance of having a placebo-controlled study and comparing this outcome to placebo.

It would be really unfortunate for somebody who has a terrible cough, who really built up a lot of hope to take a medicine, has a very small effect and may have mostly a placebo effect, and the same time then experience a side effect from something that is probably not providing something much more than placebo. So maybe some adverse effects in the people who are experiencing placebo effects is another way to think about risk-benefit.

DR. CARVALHO: Thank you.

Emma D'Agostino?

DR. D'AGOSTINO: Thank you. I think I'm thinking similarly to how others have commented. I just want to reiterate what we heard a few minutes ago about the little bit of push back on this just being a symptomatic condition. On the one hand, it's true that these patients aren't dying of cough exactly, but we heard the severe burden and the secondary conditions that develop.

So I do want to make sure it's really coming through to the agency that we're not dismissing the burden of disease here. The pain and the secondary

effects that can develop -- hernias, broken ribs, pulled vessels, and social stigma -- I don't want to brush that aside in any way. But also given how severe we heard the effects are , I absolutely agree that I would hate to build up hope for a drug that appears to have such a minimal effect.

I also have been thinking about the taste side effects a little bit differently. I feel like a 20-ish percent dropout rate due to that AE is quite high. It's true that I don't think there's really a safety concern, but if that many patients are dropping out in the trial, one, if they were feeling so much benefit, would they have dropped out? And two, if that's how many are dropping out in the trial, I would expect to see a bigger dropout rate in real world. So that has been really in the back of my mind as I've been going through and thinking through this data. I would really worry about what the drop-off rate would be and whether people would really stay on drug if this were to go on to market.

DR. CARVALHO: Thank you, Dr. D'Agostino.

Ms. Schwartzott?

MS. SCHWARTZOTT: I've also been thinking about other recent medications that have been in and out of market. There are the risks of the medication, but there's also a risk with the FDA of whether or not to put through certain drugs that are on the bubble of whether or not they have efficacy. Some recently have been suggested to remove them, so we have to be mindful of that.

For this particular drug, I do not see a major risk. I think we need to also weigh the risk for the patients who continue to go without treatment. They're at risk just for not getting treatment, and if this is just a small amount of treatment and also a psychological treatment, then it's something. But I think it's very important to continue to follow this medication, follow trials, and if it goes right to the market, follow the patients and determine whether or not it should stay on the market.

I also think that the companies need to find a better solution that does have better outcomes, and figure out what those outcomes are. But the risk

itself to the patient, I think it should be up to the patients because it's something that's not permanently damaging. And if they find benefit, they should be able to have their chance at that benefit, and if they find out it doesn't work, then they can easily remove it from their treatments. Thank you.

DR. CARVALHO: Thank you.

Dr. Kelso?

DR. KELSO: So I just want to say that I also was very moved by the thoughtful and articulate patients who commented during the public comment period and am in no way minimizing the seriousness and the life-changing impact of this condition. But I think having said that, that just makes it even more important that we're careful to only offer people a medication that has a real chance of making a real improvement in their condition. So I absolutely appreciate the seriousness of the condition and the absolute need for an effective treatment. I just don't think that this has been demonstrated to be such a treatment.

DR. CARVALHO: Thank you, Dr. Kelso.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. Sally Hunsberger. What I've heard is that people could go on the drug, and then if they don't have an improvement and they have the taste effect, they could drop off. But my concern is if you look at the curves, the placebo curves go down in the first 4 weeks just like the treatment does, so you won't know if you're having a placebo effect or if you're having a treatment effect; so then people would continue on this drug just because they're having a placebo effect.

So I think that huge placebo effect is a real problem, given the very small drug effect, and I don't think we'll be able to say, "Oh, they're not getting an effect, so they'll just stop." So I do think this benefit-risk is a problem. Thank you.

DR. CARVALHO: Thank you.

Any other comments from the panel?

(No response.)

DR. CARVALHO: Hearing none, I'm going to attempt to summarize what's been said over here. Again, everybody is in agreement and complete

concordance that this is actually a pretty terrible condition, and the situation where it's not just a symptom, but it has a severe burden of disease, other repercussions with other conditions, and really is effects versus quality of life, not to mention just even the social stigma that may go along with this; yet, we want to do right by these patients, and we want to make sure that what is recommended is something that we are convinced that it's going to help them. There is also the flip side of the coin that we have to weigh the risks for patients who remain untreated. They, too, will have a risk that is ongoing.

There is a small but uncertain benefit balanced with a mild-to-moderate reversible side effect. A panelist made a comment that a longer period could be considered to watch these patients and, again, the concern about the mirroring of the placebo effect in the curve with the drug effect and are these patients having a placebo effect that is, at periods of time, more significant than the drug effect.

Any other comments from the panel?

(No response.)

DR. CARVALHO: And if not, we'll go on to question 3, and question 3 is a voting question. Question 3, does the evidence demonstrate that gefapixant provides a clinically meaningful benefit to adult patients with refractory or unexplained chronic cough, given the small reduction in cough frequency and results from PROs?

Also, once you vote, please provide a rationale for your vote. If you conclude that there is insufficient evidence of a clinically meaningful benefit, describe the evidence that could be collected to show a benefit that is clinically meaningful, and we'll open it up for panel discussion.

DR. STEVENSON: Hello, Dr. Carvalho. This is Takyiah speaking. Before we go into discussion on the wording of the question, I'm just going to read the voting instructions to the panel.

DR. CARVALHO: Oh, please.

DR. STEVENSON: Thank you, Dr. Carvalho.

Question 3 is a voting question. Voting members will use the Zoom platform to submit their vote for this meeting. If you are not a voting member, you'll be moved to a breakout room while we conduct the vote. After the chairperson reads the vote question into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce that voting will begin.

A voting window will appear where you can submit your vote. There will be no discussion during the voting session. You should select the button in the window that corresponds to your vote: yes, no, or abstain. Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will announce that the vote is closed. Please note there will be a momentary pause as we tally the vote results and return non-voting members to the meeting room.

Next, the vote results will be displayed on the screen. I will read the vote results from the

screen into the record. Thereafter, the chairperson will go down a list, and each voting member will state their name and their vote into the record. Voting members should also address any subparts of the voting question, including the rationale for their vote.

Are there any questions about the voting process before we begin?

(No response.)

DR. STEVENSON: Since there are no questions, I will hand it back to Dr. Carvalho, and you can begin.

DR. CARVALHO: Okay. The voting question has been read, and if there are questions about the voting of the question, we can open it up for discussion. If not, then we can go ahead and begin voting.

(No response.)

DR. CARVALHO: Dr. Stevenson, you're muted.

DR. STEVENSON: Sorry. If there are no questions about the wording, we will now move non-voting participants to the breakout room.

(Voting.)

DR. STEVENSON: Voting has closed and is now complete. The voting results will be displayed.

(Pause.)

DR. STEVENSON: There is 1 yes, 12 noes, and zero abstentions. I will hand it back to the chair.

DR. CARVALHO: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also state the rationale for your vote. And we'll start with the first person on the list, and that is Dr. Courey.

DR. COUREY: Hello. I wish I could have voted yes, but the balance of the literature suggests that patients with chronic non-specific cough will have a response to treatment up to 50 percent, regardless of the type of treatment you give them. You have a group of motivated patients who want to participate in the study trial, and they go through all of the pains, and you have a 57 percent response rate among patients on placebo, the subjects on placebo, and a 63 percent response rate in the

patients on drug. I don't think that is a significantly big change over what's to be expected.

In addition, two-thirds of the patients on medication had some sense that they were on the medication, so that would affect their expression of cough symptom severity or frequency and their reports on the patient-reported outcome measures. Given all of that, I don't think the level of evidence supports that the drug makes a significant difference. It's unfortunate. I am concerned that if the drug is readily available, it could lead to a delay in diagnosis of other things, other illnesses, because cough, while it can be very debilitating, is a symptom, not a disease in and of itself. So I think this would delay the evaluation of the patients for other diseases and could be potentially harmful that way.

We need a more objective measure of cough frequency and severity. If there is a way of objectifying urinary incontinence and starting with a severe group of patients who have urinary incontinence, perhaps you could use that. If there

is a way of using the recordings that we could judge cough severity based on volume or intensity of the sound, as well as length of the coughing episode, that might be a way, or direct observations of the patients before, and then 3 or 4 weeks after being on medication or placebo, as long as we could give them a placebo that created a similar taste disturbance. Thank you.

DR. CARVALHO: Thank you, Dr. Courey.

I'm next. I also voted no, and I very much had wanted to vote yes. I agree with other comments the panel members have made, including how huge of a burden of disease this is and how really we do need to keep trying.

Getting some endpoints, and getting perhaps different timings, and perhaps time the result of different symptoms, as Dr. Courey mentioned, with cough and urinary incontinence, and keeping on with trying to find a solution for these patients because this is going to be hugely important. Thank you.

Dr. Bacharier?

DR. BACHARIER: Leonard Bacharier. I

similarly voted no, despite my wish to have been more positive. I was largely influenced by the inconsistency in the primary outcome after the validation of the primary outcome capture system led the second trial to not meet nominal significance. I think we're really at a loss for what an outcome really would compel us that an agent in this condition made our patients meaningfully and predictably better.

As mentioned earlier, I think the risk profile on the patient level is actually pretty low. I wasn't terribly concerned about the risk of unblinding because I don't think that was the driver here. I think the driver of all we saw here was a very robust placebo effect amongst a group of highly motivated patients, more so than anything else.

I think that the issue here really is studying these not quite orphan conditions, but these conditions that don't have robust pre-established outcomes. And I applaud the sponsor for doing their very best to try to get at this, but I think we need a better outcome measure that I think more completely

captures what we've heard throughout the day about the various aspects of this disease, and I'm not sure I know what that is. But I do have a sense that this discussion should have shined some light on where the clinically meaningful aspects might be, and I think further work to further refine those and then study those is important.

My heart goes out to this patient population who remain hopeful for a therapy that would make a difference, but I am just concerned that we don't want to be providing just hope. We want to be providing predictably effective pharmacologics that are likely to make meaningful differences, and I am, like many of the group, concerned that the magnitude of effect, given all the other factors, was just less than would have been more compelling. So I'll stop there. Thank you.

DR. CARVALHO: Thank you, Dr. Bacharier.

Next is Dr. Garibaldi.

DR. GARIBALDI: Hi, everyone. This is Brian Garibaldi. I, too, voted no, and I think really what it came down to for me was, yes, there is a small

benefit with some uncertainty as to the cause of that benefit. I think we've recognized that the PRO tools, in particular, we have are imperfect and probably need to have better anchors. I think, as Dr. Bacharier and Dr. Courey mentioned, we do need to have better markers of efficacy just beyond median or mean cough per hour percent change in frequency of cough.

My hope, from the data that's already been presented and from the validation of being able to quantify cough, is that some of that data may already be available to try to better align with PROs and really come up with a better assessment of what's actually happening in terms of changes; and not just frequency of cough, but character durations vary in ways that may be quantifiable that can get around the placebo effect that we saw.

I struggled also with the fact that almost 70 percent of patients probably knew they were having a side effect. That happens very commonly in patients on drug. That happens in many patients within two days of taking the drug, and I think that

makes it really hard to know exactly what's driving that small difference between the placebo group and the folks who got drug. And again, when we're thinking about risk-benefit, I think we would all agree that if you set out to design a drug that was going to be efficacious in this disease, you'd hope for a much more robust effect above and beyond what you get from the placebo effect. I know we didn't get that here, and trying to manage that disappointment and really balance what the true effect is versus the the small risk profile, I think that was really challenging.

So I wanted to vote yes for a number of reasons that have already been discussed, but I think right now the data is not where I feel that this should be something widely available and used for patients with this chronic and debilitating condition.

DR. CARVALHO: Thank you, Dr. Garibaldi.

Next is Dr. Hamblett.

DR. HAMBLETT: Thank you. I also voted no for three primary reasons, one being the overall

small meaningful effect with the cough frequency; second was the lack of consensus between the sponsor and the agency regarding the meaningful of the PROs; and then third, just the inability to conclude that the small differences aren't due to the unblinding.

I think when we think ahead in terms of what data do we need, I think as long as we have a study drug that is at risk for potentially unblinding, then we need designs and we need endpoints that are robust to that. Maybe it's taste matching, and if that's not feasible, then we really do need to invest in more objective endpoints. I think the PROs are extremely important, but when there's that risk of unblinding, we're also going to need to invest in those objective endpoints. I think Dr. Courey mentioned is there an objective measure of incontinence, and so forth. I'd also like to see moving towards consensus on the meaningfulness of the PROs. If it's not these PROs, is there another fit-for-purpose PRO that needs to be developed, specifically for this population?

But lastly, I just want to conclude that it

is very disappointing to vote no; however, I just want to speak to the value of these trials and to everyone who participated in them because I do feel like they provide a road map for how we are going to develop these therapies moving forward. So thank you to our community that participated in these trials.

DR. CARVALHO: Thank you, Dr. Hamblett.

Dr. Coon?

DR. COON: Hi. Cheryl Coon. I wish that these trials showed us the therapy that patients are desperately waiting for, but I also had to vote no. Only one of the two adequate and well-controlled trials achieved statistical significance on its primary endpoint, and the effects appeared to be small. Small effects can certainly be meaningful, but there is an absence of data indicating so. I appreciate what the committee's patient representative said in the discussion around question number 1, that a small benefit can make a big difference in the quality of life to patients. I absolutely agree with that and, unfortunately, that's where the evidence is lacking.

So regarding the evidence that could be collected to show a benefit is clinically meaningful, in an ideal world, I'd like to see interviews done with the individuals who have the experience on the therapy to understand if the changes that they experienced in the cough frequency and in other outcomes were meaningful to them and how, putting it into kind of that metric of how is this impacting your your daily life? Are you able to get back to the things that you've had to give up, given your chronic cough condition?

In these interviews, you could also gain an understanding of what changes are meaningful on the PGIF and PGIC to inform anchor-based analyses and to help inform that discussion in the future between the sponsors and FDA, and then there could also be a gain in understanding the impact of, in this case, taste-related disturbances and how tolerable the treatment would be considered in a long-term setting. Thank you.

DR. CARVALHO: Thank you, Dr. Coon.

Miss Schwartzott?

MS. SCHWARTZOTT: Well, I voted yes, but I will admit I was greatly on the fence, and I was really wishing there were other options. I am a patient, so I have a different viewpoint than everyone else, but I've been debating to myself what level of effectiveness should a medication have to recommend it to go to market. With this drug, any reduction of cough symptoms for many patients would be worthwhile to them, as long as the risk is low, which I felt that it was.

I wanted to give the patients a chance to give them something that could potentially work, at least a little bit, until the perfect drug comes along, which hopefully won't be that far from now, but I also felt that the medication would need much further study, which is why I was on the fence about voting yes, and it needs follow up. The protocols need more definition, as we've discussed.

I hope that the company and other companies are going to see the benefit of this and see the need, and continue to work to help these patients because they deserve a cure, or at least a treatment,

and sooner rather than later. Thank you very much for everybody who's put thought into this.

DR. CARVALHO: Thank you, Ms. Schwartzott.

Next is Dr. Kim.

DR. STEVENSON: I'm so sorry to interrupt, Dr. Carvalho. This is Takyiah speaking. Just a friendly reminder to the panel to please state your full name and your vote for the record. Thank you so much.

DR. CARVALHO: Thank you, Dr. Stevenson.

Dr. Kim?

DR. E. KIM: Edwin Kim, University of North Carolina, and I voted no. My rationale is it seemed that participating in the clinical trial provided a benefit, but specifically reading the question of does the evidence demonstrate that gefapixant provide the benefit, that's where I get stuck. With the large placebo effect, it's hard to differentiate how much effect the medication itself provided. Similarly, with the PROs, there might be some benefit, but it seemed to be similar in the placebo, as well as in the actual treatment group. So not

being able to differentiate a compelling difference from the treatment from placebo is why I voted no.

Moving forward, that would be the recommendation. Is there a way to separate out the placebo effect from the treatment itself? Whether that might be in a clinical trial design, or I'm not sure if some sort of crossover design or something like that might be able to tease out placebo versus an actual medication effect.

More specifically, there's been discussion about outcomes, and in my mind, I do wonder about going back to actually how the medication is supposed to work. It's supposed to suppress cough, so I wonder if outcomes could be more built around that. Perhaps there could be a type of study or outcome that is actually measuring response to triggers. Many of the patients described certain situations, triggers, whether it's perfume, dust, and things along those lines that would reliably trigger cough. So perhaps that would be a way to really demonstrate that the medication itself, more than a placebo effect, is actually making a difference and

decreasing that frequency of cough. And then perhaps there could be further correlates to the other quality-of-life type metrics. Thank you.

DR. CARVALHO: Thank you, Dr. Kim.

Dr. Rank?

DR. RANK: Matt Rank. I voted no. I want to thank everybody for excellent presentations, particularly the patients who spoke at the open public forum. My vote is driven by the small and uncertain benefit of the intervention, relative to the placebo; the overall small effect size; the uncertainty and consistency across both the primary outcomes, across pivotal trials, as well as the uncertainty about the PROs.

Moving forward, I had similar thoughts to what Dr. Kim had articulated just before me, that very, very large placebo response I think is something that needs to be understood, and I think study design, perhaps run-in, perhaps cross. There may be some ways to either exclude people who are likely to have a large placebo effect, and then narrow down the patient section, where you're getting

people who have potentially the benefit from a drug like this, or other future drugs, and be able to measure that more clearly. Thank you.

DR. CARVALHO: Thank you, Dr. Rank.

Next is Dr. D'Agostino.

DR. D'AGOSTINO: Thank you. Emma D'Agostino. I voted no for all the reasons that we've heard. The small decrease in both the objective and subjective measures were really what drove my vote, particularly when considering the responses paired with a high placebo response, and just were not enough, to me, to demonstrate clinical meaningfulness.

I also was really thinking about the two-thirds or so of patients that experienced taste AEs, and even though I absolutely agree that this drug would be safe, with a 20 percent dropout rate in the trial, I'm not sure how that would really translate to use in the clinic if you have a drug with a pretty small benefit and what appears to be a real tolerability issue.

Then moving forward, as we've heard from others, really thinking about rethinking the endpoint

to capture what's most meaningful to patients, so rethinking that cough frequency instead of looking at overall frequency through 24 hours, and looking at cough clusters and something to really capture the most meaningful manifestations of cough. Then I agree on taking a closer look at urinary incontinence. I think in the sponsor's documents, the sponsor briefing that we had -- sorry, in the FDA briefing that we had, we saw language that there was a little bit of skepticism in the use of urinary incontinence as an outcome specific to cough, but I do want to just put it out there that I have someone with a different cough condition. I would assert that if we saw a reduction in cough specifically, I would absolutely expect to see a reduction in urinary incontinence, so I would put that as a highly meaningful endpoint, especially given what we heard from the patients today.

Then one other piece that we didn't talk about at all today, but I was struck by just reading all the data, was we had 52-week endpoints for all of the PROs, but not any of the objective endpoints. So

it would have been nice, especially for the 027 study, to see objective data beyond 12 weeks, which of course we can't go back and redo, but I would have loved to have seen some durability beyond 12 weeks. I think that was everything that I was thinking about.

DR. CARVALHO: Thank you, Dr. D'Agostino.

Next is Dr. Evans.

DR. EVANS: Yes. Hi. This is Scott Evans, MD Anderson. I voted no. I am surprised at the outcome of the vote and how dramatic it is, considering how much I struggled with this vote. I do think that the count data is likely valid, and I do think this agent likely does something. But at the end of the day, I struggled with the small effect size relative to the placebo effect and the apparent lack of correlation, at least clear correlation, with the PROs. That's what drove my vote.

I am a pulmonary clinician. I see patients with chronic cough. I understand the need. I am sympathetic to the folks that presented today, but I do want to be careful and resist my own urge to think

that something is better than nothing because I think we are establishing precedence here, and if we adopt the wrong markers and outcomes, I think we actually may limit our ability to identify the best drug, and that's my comment. Thank you.

DR. CARVALHO: Thank you, Dr. Evans.

Next is Dr. Hunsberger.

DR. HUNSBERGER: Sally Hunsberger. Everything that's been said, I totally agree with, so I will just go rapidly through. I just want to thank the sponsor for doing this study. I think all of them were were really well-designed studies. Unfortunately, the placebo effect was so large that it made it difficult to really be able to interpret the data. I appreciate the speakers, and it really helped me to to understand the problem, and the FDA's report I think was really helpful.

I think the science here is really strong. I hope that this no vote doesn't discourage the continued search for treatment for this population, and I do think that what we need is better endpoints that better match what the public speakers said were

the issues, and maybe then we will be able to see an effect. So that's really all I have to say. Thank you.

DR. CARVALHO: Thank you, Dr. Hunsberger.

And last is Dr. Kelso.

DR. KELSO: John Kelso at Scripps Clinic. I voted no because the prespecified primary endpoint was achieved in only one of the two studies because the absolute treatment effect, the difference in cough counts, was so small that it is likely not of clinical significance. In terms of trying to assess that clinical significance, I found the patient global impression of change data to be most relevant, where there was a virtual overlap between treatment and placebo. So it appeared that the patient's assessment was, in fact, there really was no difference in getting the drug versus placebo and about whether their impression was if they had had an improvement in their cough, which then cast doubt on that tiny absolute measured difference.

I think that the comments that have been made about other parameters that might be studied going

forward are all appropriate, but I also think that had this drug been more effective, we would have seen it in the data that was collected, so I think the right kind of data being collected in terms of counting coughs, patient coughs, and the patient-reported outcomes in terms of these cough scales and whatnot. I think if this medication had been more effective, it would have also been more apparent, even in the data that was collected in this study. Thank you.

DR. CARVALHO: Thank you very much, Dr. Kelso, and thank you so much to the FDA, and to the sponsor, and to the the panelists who were very thoughtful. They did a lot of due diligence. And all in all, we all agree that this needs to be something that we continue to pursue because we all know that these patients are highly uncomfortable, and their quality of life could be improved. Thank you very much.

Before we adjourn, are there any last comments from the FDA?

DR. CHIN: Yes. Thank you, Dr. Carvalho.

This is Stacy Chin, FDA. I just want to take a moment to thank everyone for their participation today. We recognize that chronic cough/refractory cough has incredible burden on patients, and we share everyone's goal of wanting to make safe and effective therapies available, and it's always disappointing when the results don't quite turn out as you would like. But we know it takes a lot of time and attention to participate in these advisory committee meetings. We really appreciate the thoughtful questions and discussions today, and we will take that into consideration in our review of this application and as going forward. We also found the open public hearing comments from the patients incredibly informative for our review of this application and other applications going forward as well. So thank you again for your participation.

Adjournment

DR. CARVALHO: We will now adjourn the meeting. Thank you.

(Whereupon, at 4:30 p.m., the meeting was adjourned.)