FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE (DODAC)

Friday, December 13, 2019

8:01 a.m. to 3:22 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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P R O C E E D I N G S

(8:01 a.m.)

Call to Order

Introduction of Committee

DR. CHODOSH: Good morning. Before we start, I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. I also would like to identify the FDA press contact -- excuse me if I got your name wrong -- Kristen Pluchino, if you would stand. There's Kristen. Thank you.

My name is Dr. James Chodosh. I'm chairperson of the Dermatologic and Ophthalmic Drugs Advisory Committee, and I'll be chairing this meeting. I will now call the meeting to order. We're going to start by going around the table and introduce ourselves. We'll start with FDA to my far left. Peter?

DR. STEIN: Thank you. Peter Stein, Office of New Drugs.

DR. CHAMBERS: Wiley Chambers, deputy

director, division of transplant and Ophthalmology Products.

DR. YOO: David Yoo, associate professor of ophthalmology at Loyola University, director of oculoplastic surgery.

DR. BRITTAIN: Erica Brittain. I'm a statistician, National Institute of Allergy and Infectious diseases, NIH.

DR. WENG: Christina Weng, associate professor of ophthalmology at Baylor college of Medicine in Houston, Texas.

DR. MURRAY: Tim Murray, Miami Ocular Oncology and Retina.

DR. FAJICULAY: Jay Fajiculay, acting designated federal officer for the DODAC.

DR. CHODOSH: Jim Chodosh. I'm professor of ophthalmology at Harvard Medical School, Mass Eye and Ear.

DR. KING: Tonya King. I'm professor of biostatistics at Penn State College of Medicine.

DR. STAMLER: John Stamler, clinical instructor, University of Iowa, Iowa City.

MS. SCHWARTZOTT: Jennifer Schwartzott. I'm the patient representative.

DR. BURMAN: Ken Burman, head of endocrine at MedStar Washington Hospital Center and a professor at Georgetown.

DR. GICHERU: Sidney Gicheru, private practice ophthalmologist in Dallas, Texas.

DR. LOW WANG: Cecilia Low Wang, endocrinologist, professor of medicine at the University of Colorado.

DR. HARTNETT: Mary Elizabeth Hartnett, professor of ophthalmology, University of Utah, Moran Eye Center.

MS. ATILLASOY: Morning. Ercem Atillasoy. I'm a dermatologist. I'm vice president at Merck and I'm the industry representative.

DR. CHODOSH: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are strongly held. Our goal is that today's meeting will be a fair 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, myself. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in 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're aware that members of the media are anxious to speak with FDA about these proceedings, however, FDA will refrain from discussing 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.

Now, I'm going to pass -- I hope I get your name right this time, Jay. Now I'll pass it to Dr. Jay Fajiculay, who read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. FAJICULAY: The Food and Drug Administration is convening today's meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act 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's determined that the agency's need for a special government employee's services outweighs his or her 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 discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses 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 discussion of biologics license application 761143, teprotumumab

solution for intravenous use, submitted by Horizon Pharma Ireland, Limited, proposed for the treatment of active thyroid eye disease. This is a particular matters meeting during which specific matters related to Horizon Pharma Ireland's BLA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing 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. Ercem Atillasoy is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Atillasoy's role at this meeting is to represent industry in general and not any particular company. Dr. Atillasoy is employed by

Merck and Company.

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

DR. CHODOSH: We're going to now proceed with the FDA's opening remarks from Dr. Wiley Chambers.

FDA Opening Remarks - Wiley Chambers

DR. CHAMBERS: Thank you very much. I want to start with a welcome, a very warm welcome, to all of those that are attending; in particular both the advisory committee members, as well as the special government employees that have been added to supplement the committee.

This topic is slightly different than what

is typically brought to the Dermatologic and Ophthalmic Advisory Committee, so we have added some additional people to widen the expertise of the group. Everybody's voice is important, and we encourage everybody to speak up as we go through.

Just to let you know where we stand with this particular application, it is a biologic license application. The discipline reviews are currently ongoing. We have made no final decisions from any discipline on any aspect of the application. This is part of the review process. You will not hear tomorrow that the application has been approved, not approved, or any kind of other. It's still all ongoing, which is why we're encouraging comments at this point in time.

Today's meeting, we're just going to discuss clinical issues. There are still manufacturing inspection reviews that we're not going to discuss and that may or may not have issues. We're not going down that road; all of which are important for any ultimate regulatory action. But there are various questions that we have that we're asking

people to comment on. We think there may be answers to some of the questions. We think there may not be answers to some of the questions, but if you have them, we'd like to hear them. And just as a final comment, if you haven't heard me say it already, we encourage all comments. Thank you very much.

DR. CHODOSH: Thank you, Wiley.

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 it's important to understand the context of an individual's participation.

For this reason, 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 sponsor, including equity interests and those based upon the

outcome of the meeting.

Likewise, 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 the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. We are now going to proceed with Horizon Pharma Ireland, Ltd's presentations.

Applicant Presentation - Timothy Walbert

MR. WALBERT: Good morning. I want to thank the chair, the panel, the FDA, and members of the public, especially the patients who are here today. I'm Tim Walbert, chairman, president, and chief executive officer of Horizon Therapeutics. I'm also here as a member of the rare disease community.

I live with both a rare disease and an autoimmune disease, and, unfortunately, my son also suffers from the same rare disease. As a result, I know firsthand the importance of bringing new therapies forward to patients.

Living with chronic conditions is a daily struggle, but it's also the reason behind why I do what I do. I personally understand what it means to have access to therapies that can significantly improve the daily life of a patient, including both myself and my son. I credit my diagnosis as the force behind me building a company culture that does whatever it takes to develop new therapies for rare diseases, and at Horizon, we believe science and compassion must work together to transform the lives of patients.

Of the more than 7,000 rare diseases in the world, only 5 percent have approved treatments. We believe teprotumumab can be one of these treatments. The initial journey for teprotumumab actually started with studies in oncology, where it was studied as a non-cytotoxic targeted therapy.

While teprotumumab was not shown to be efficacious in oncology patients, it did have a reassuring safety profile, which was further supplanted by safety data from other drugs with the same mechanism of action. Based on this, it was an

excellent candidate for use in a different indication.

Given the emerging body of data regarding the mechanistic underpinnings of thyroid eye disease and the potential relevance of teprotumumab's mechanism of action, the IND for teprotumumab in thyroid eye disease was established in 2011. In 2013, teprotumumab was awarded orphan drug designation for active thyroid eye disease, as the annual incidence is less than 25,000, and approximately 75,000 patients are living with active thyroid eye disease in the United States today.

In this same year, the first patient was enrolled in study 1 with thyroid eye disease. In 2015, teprotumumab was awarded fast-track designation, and the last patient in study 1 completed their 24-week visit. The results of study 1 were statistically significant, clinically meaningful, and were the first demonstration of the potential for teprotumumab in the treatment of this disease.

The FDA granted breakthrough designation in 2016 in the recognition of the seriousness of thyroid eye disease, the level of unmet need, and the potential of teprotumumab to deliver substantial benefit. In August 2016, an end of phase 2 meeting was held with the agency, where design of the confirmatory study, or study 2, was discussed. In May 2017, the results of study 1 reported in the New England Journal of Medicine, and Horizon acquired teprotumumab.

We initiated the confirmatory study, study 2, that same year. We rapidly enrolled study 2, and early in 2019, the last patient completed their 24-week visit. In July, we submitted the biologic license application for what we hope will be the first FDA-approved therapy for patients living with thyroid eye disease and that of course brings us here today to present the results of our clinical program to you.

Overall, the results show that teprotumumab was effective and generally well tolerated, with a positive benefit-risk profile across two

well-designed clinical studies and provided clinically meaningful improvements across multiple facets of this rare debilitating disease for which there are no approved treatments.

For the agenda for today's presentation, Dr. Raymond Douglas will discuss the unmet need for new therapy to treat patients with thyroid eye disease. Dr. Shao-Lee Lin will then discuss the teprotumumab mechanism and the program overall of teprotumumab in more detail. Dr. Liz Thompson will review the efficacy and safety results for a clinical development program, and then Dr. Douglas will close our presentation by providing his clinical perspective on teprotumumab in thyroid eye disease.

We also have additional experts here with us today, and we'll note that all outside experts have been compensated for their time and travel for today's meeting. Thank you, and I'll now turn the presentation over to Dr. Douglas.

Applicant Presentation - Raymond Douglas

DR. DOUGLAS: Good morning. I am Raymond

Douglas, and I am pleased to be here to discuss the urgent need for an effective and well-tolerated treatment for patients with thyroid eye disease. By way of background, I am an ophthalmologist and an oculoplastic surgeon, and the director of the Orbital and Thyroid Eye Disease program at Cedars-Sinai Medical Center in Los Angeles. I'm also the co-founder of the International Thyroid Eye Disease Society, or ITEDS.

I was involved in the translational science that led to the clinical studies of teprotumumab. In addition, I served as the principal investigator throughout the clinical development program for teprotumumab, which is the largest clinical program conducted in thyroid eye disease.

Thyroid eye disease, although commonly associated with Graves' disease, is a distinct disease. Treatment of Graves' disease doesn't treat thyroid eye disease. In fact, one of the treatments for Graves' disease, radioactive iodine, can induce or exacerbate thyroid eye disease. Thyroid eye disease also occurs in patients who are

euthyroid or hypothyroid.

So what is thyroid eye disease? Thyroid eye disease is a rare, progressive, vision-threatening autoimmune inflammatory disease that attacks the tissue behind the eye, pushing the eye forward out of the socket. Importantly, this interaction occurs behind the eye and not within the eye itself. This disease has the potential for visual impairment based on a variety of causes, which I will discuss in detail.

Thyroid eye disease impacts more women than men. There are generally two peaks of incidence with thyroid disease. The first typically occurs in a patient's forties. The second is in their sixties for women and a little later for men. Like many rare diseases, we have limited published epidemiological data.

Based on what is available and the current U.S. population numbers, the incidence of active thyroid eye disease is estimated at less than 25,000 patients annually, with an estimated prevalence of 75,000 patients. There's no

significant ethnic predisposition, and smoking worsens the severity of the disease.

Let's review the natural history of thyroid eye disease. Thyroid eye disease involves an initial progressive worsening of signs and symptoms during what is referred to as active disease. This involves visible signs of inflammation, which can last up to three years. During active disease, patients can develop proptosis lid retraction, and double vision.

Inflammatory signs and symptoms generally diminish, but the proptosis, diplopia, and disfigurement persists based on the remodeled orbital structures. Once the inflammation has resolved, patients are called inactive. Eventually, remodeled tissues become fibrotic, leaving patients with significant irreversible residual structural damage.

It's important to note that thyroid eye disease is a spectrum and is different for each individual. During active thyroid eye disease, patients may present with orbital pain, periorbital

edema, proptosis, eyelid retraction, strabismus, double vision, and facial disfigurement. In severe cases, patients experience optic neuropathy and blindness. Many of these symptoms persist in inactive thyroid eye disease.

Proptosis, or bulging of the eye, is one of the most disfiguring and prevalent signs of thyroid eye disease. Proptosis results from an expansion of soft tissue and muscle tissue posterior to the eye due to inflammation, edema, proliferation, and higher on end deposition. Proptosis is a primary driver of morbidity in this disease state.

Excessive proptosis impairs a patient's ability to blink or close their eyes at night. This results in pain and potentially corneal ulceration. In fact, many of my patients need to wear sunglasses during the day due to photosensitivity, and at night, as shown in the picture to the right, bandages over their eyes are often needed in order to sleep because they can't shut their eyes. In addition, there can be profound changes in facial appearance, which in

addition to the functional impairment can also have profound social consequences.

Diplopia or double vision is another common symptom that significantly impairs daily living. Patients with double vision see more than one image of a single object as a result of misalignment of the eyes. It is often associated with headaches and even a feeling of nausea while trying to perform simple daily tasks. These patients with double vision have difficulty working, driving, and performing simple tasks such as working on a computer.

The clinical manifestations of thyroid eye disease negatively impact a patient's quality of life. These include disturbances in visual function and activities of daily living such as driving, reading, and even moving around the house and ambulating. These patients often have facial disfigurement leading to social isolation and a fear of being seen in public.

There are currently no FDA-approved treatments available for patients with active

thyroid eye disease. Likewise, there are currently no U.S. based treatment guidelines. The reality is that we have few things that we can do for our patients. In fact, we're still searching for a, quote, "standard of care."

The reality is that the current use of glucocorticoids is often debated. Glucocorticoids are used at a very high intravenous dose, up to 8 grams, to address inflammatory signs and symptoms. Steroids can decrease the number of short-term inflammatory signs or symptoms a patient has, but there's no evidence that they have a meaningful impact on proptosis.

The use of high-dose corticosteroids is fraught with substantial life-threatening side effects. Hyperglycemia, new onset diabetes, liver toxicity, and in rare cases, sudden death are reported. Furthermore, upon discontinuation, up to 40 percent of patients have a rebound of inflammatory signs and symptoms. Because of the substantial short- and long-term side effects of steroids, physicians like myself often choose to

watch and wait while inflammatory signs diminish. It is not until the disease stabilizes that we can consider surgical treatment.

There are additional therapies for active thyroid eye disease that can be characterized as exploratory and are utilized off label. None have been shown to impact proptosis and diplopia. All of these treatment approaches have side effects that can be difficult to manage and poor efficacy. And while they can impact the inflammatory signs, they do not treat proptosis or double vision, the most severe consequences of thyroid eye disease.

A common non-pharmacological method for treating active thyroid eye disease is orbital radiation, which has complications such as cataract, retinopathy, and dry eye. Once thyroid eye disease is inactive, surgery is considered the only option to try, in part, to address its clinical manifestations and consequences. A patient typically needs to wait until the inflammation has abated to avoid any exacerbation of inflammation before undergoing staged and

multiple surgeries.

Orbital decompression involves removal of fat and bone from behind the eye to correct the proptosis. In a staged manner and after several months of healing, strabismus surgery is then performed to realign the eyes. Eventually, again, after months of healing, eyelid surgery is done so the eyes can properly close. Accumulation of fibrotic tissue behind the eye complicates these operations and severely limits their benefit.

While staged surgery is corrective for some, it can result in permanent eye misalignment, double vision, and sight impairment. In addition, sinusitis, orbital hemorrhage, cerebral spinal fluid leak, meningitis, and, in rare cases, death can occur from these surgeries. These surgeries are not trivial. Most importantly, even after multiple surgeries, patients are not restored to their pre-disease state.

In closing, thyroid eye disease is a debilitating, vision threatening, and disfiguring disease. I treat these patients every day, but my

options are poor. Ideally, we would have an efficacious treatment that would decrease inflammatory signs of thyroid disease, reduce proptosis by at least 2 millimeters, which is clinically relevant for this disease because it's expected to improve eyelid closure, coverage over the cornea, reduce double vision, and improve quality of life, all with manageable side effects.

I showed you this graph earlier. Our ideal therapy would reset the disease course as shown in this added curve. By doing so, we would improve patient function, appearance, and wellbeing, and potentially eliminate or minimize the need for surgical interventions.

However, the reality is that the options that we are currently using do not reverse the underlying alterations of orbital tissue or reverse proptosis, a major driver of morbidity in this disease. They do not modify the disease and they often have very substantial side effects.

What you will see throughout today's presentation is that teprotumumab is different.

You'll hear data on the potential of teprotumumab to reverse this disease and fulfill this unmet need, both from its mechanism of action and the results of the clinical program. Thank you, and I will now turn the lectern to Dr. Lin.

Applicant Presentation - Shao-Lee Lin

DR. LIN: Thank you Dr. Douglas, and good morning, everyone. I'm Shao-Lee Lin, head of R&D, and chief scientific officer at Horizon. Given the high unmet need that Dr. Douglas just described, I'd like to take a few moments to discuss the pathophysiology of thyroid eye disease; share the relevance of the mechanism of action of teprotumumab; and provide an overview of the clinical program of teprotumumab for the treatment of thyroid eye disease.

Thyroid eye disease is an autoimmune disease, and its pathology occurs in the tissues behind the eye. On the left panel is a representation of a healthy eye, and on the right, a representation of active thyroid eye disease and the structural changes that occur in the tissues

behind the eye, driven by both immune-mediated and mechanical processes. These include immune cell infiltration, production of cytokines and chemokines, and all result in inflammation and redness.

Additionally, accumulation of hyaluronic acid and adipogenesis causes enlargement of extra ocular muscles and expansion of the orbital tissue. In fact, these events result in increased intraorbital tissue volume that leads to forward displacement of the eye, which drives proptosis, strabismus, and compression of the optic nerve, which can lead to optic neuropathy. Although inflammation diminishes over time, these structural changes have the potential to become irreversible due to the fibrosis of the tissue and can result in permanent facial disfigurement.

IGF-1 receptor mediated signaling driven by auto antibodies has a central role in driving the pathogenesis of this disease behind the eye. As is seen with other autoimmune conditions, autoantibodies play a major role in driving thyroid

eye disease. In Graves' disease, for instance, it's well established that hyperthyroidism is driven by auto antibodies to the TSH receptor.

On the other hand, thyroid eye disease can occur in the absence of Graves' disease and without detectable TSH receptor auto antibodies. In fact, it was initially observed that IGF-1 receptor is overexpressed in postsurgical tissue from thyroid eye disease patients, and hence, it was postulated that IGF-1 receptor plays a central role in the disease pathogenesis, with autoantibody signaling through the IGF-1 receptor and TSH receptor complex. And indeed, it's been demonstrated that autoantibodies from thyroid eye disease patients can displace IGF-1 binding to the IGF-1 receptor in orbital fibroblasts and trigger a signaling cascade.

This results in the production of inflammatory cytokines, chemokines, accumulation of hyaluronic acid, and extracellular matrix deposition, and drives adipogenesis. As I noted earlier, these components are responsible for the

inflammation and remodeling of the orbital tissue, causing proptosis and other clinical signs and symptoms observed in thyroid eye disease and eventually leading to fibrosis.

The prominent role of these events in the pathogenesis of thyroid eye disease suggests that it is biologically plausible to modify the course of the disease by inhibiting IGF-1 receptor. This is in fact supported by ex vivo evidence with orbital fibroblasts from thyroid eye disease patients.

In the figure on the upper right, you can see when orbital fibroblasts from thyroid eye disease patients are exposed to autoantibodies from patient's sera, there's an increase in inflammatory cytokines, such as RANTES, shown in the middle bar, and as compared to control sera, which is shown on the left. This effect can be blocked upon addition of anti-IGF-1 receptor antibody, shown on the far right. Similar results with IGF-1 receptor blockade have been seen with other inflammatory cytokines such as IL-16, IL-6, and TNF alpha, all

not shown here.

Autoantibodies can also increase hyaluronic acid concentration, which is shown in the middle bar on the bottom graph, and as compared to control, again on the left, and is also blocked upon addition of anti-IGF-1 receptor antibody, as seen on the right. Taken together, these data demonstrate that IGF-1 receptor inhibition can block key components in the pathogenesis of thyroid eye disease.

To tie this all together, based on these data, autoantibodies signal via IGF-1 receptor, driving pathogenic processes behind the eye and resulting in thyroid eye disease, and these effects can be blocked by IGF-1 receptor inhibition. Teprotumumab, a fully human monoclonal antibody, targets and binds the IGF-1 receptor, displaces IGF-1 and 2-ligand binding to the receptor, blocking IGF-1 receptor mediated downstream signaling. Teprotumumab also downregulates cell surface levels of the receptor.

As mentioned by Dr. Douglas, steroids are

among the current treatment options to manage thyroid eye disease. The mechanism of action of steroids includes pathways that broadly impact gene expression and translation. Because of the wide-ranging effects of steroids, the adverse event profile for steroids, especially at the high doses that Dr. Douglas described, is of substantial concern for serious side effects.

Importantly, steroids do not address the underlying mechanistic drivers of thyroid eye disease and are notably not effective at reducing proptosis. In contrast, as a targeted anti-IGF-1 receptor agent, teprotumumab is expected to block inflammatory cytokine production, hyaluronic acid accumulation, and adipogenesis. These effects, in turn, are expected to reverse tissue expansion and thereby improve proptosis.

Importantly, it's also expected to impact progression of tissue remodeling and prevent or minimize the potential for permanent damage due to fibrosis and scarring. Collectively, this provides evidence that disease modification with IGF-1

receptor blockade is biologically plausible, which is most importantly consistent with the clinical data seen with teprotumumab treatment in patients with thyroid eye disease.

I would now like to share with you a high-level overview of the history of teprotumumab and the clinical program in thyroid eye disease. Teprotumumab was initially developed for use in oncology. In fact, it was one of several antibodies to IGF-1 receptor that were investigated in oncology. As a class, their promise was that they would be non-cytotoxic targeted therapies that could be efficacious in cancer, based on the role of IGF-1 in tissue growth and differentiation and, unfortunately, that promise wasn't clearly borne out in oncology.

As a class, there was a significant amount of clinical experience. The most notable and consistent finding was the emergence of hyperglycemia, which appeared as a generally manageable side effect across the class. Most reported cases were mild or moderate and were

reversible. Published manuscripts in peer-reviewed literature discussing teprotumumab's oncology program described it as a well-tolerated therapy with no dose limiting toxicities identified.

The teprotumumab clinical program in oncology included 9 clinical studies in patients with a variety of advanced malignancies. Overall, a total of 727 patients were exposed to teprotumumab in the oncology setting. These were at dose levels, ranging from 1 to 27 milligrams per kilogram and durations ranging from weekly to every 3 weeks.

In addition, although one study was single arm, it's important to note that the oncology indications were late stage and heterogeneous. These patients were very sick, and most had prior or ongoing exposures to cytotoxic agents. Hence, per agreement with FDA, our BLA submission for teprotumumab in thyroid eye disease contained a separate summary of the oncology data.

That said, despite this very sick patient population, the overall safety profile in oncology

appears consistent with that found with the thyroid eye disease population, and both will be covered by Dr. Thompson during the safety portion of this presentation.

The dose regimen for teprotumumab in thyroid eye disease was initially selected based on learnings from the oncology program. Pharmacokinetic analyses from dose-ranging studies in oncology indicated a predominant role of target mediated clearance at low doses of teprotumumab. Accordingly, we selected a dose regimen in study 1 that provided serum concentrations maintaining greater than 90 percent saturation of IGF-1 receptor throughout this dosing interval.

This regimen was 10 milligrams per kilogram for the first dose, followed by 20 milligrams per kilogram every 3 weeks for the remaining 7 infusions. This first dose of 10 milligrams per kilogram was to assess tolerability of teprotumumab before escalation to 20 milligrams per kilogram for all subsequent infusions.

The results of study 1 demonstrated that

this regimen was effective and well tolerated, and therefore provided justification for continued evaluation in the confirmatory study 2. The overall data from the development program in thyroid eye disease supports the recommended teprotumumab dosing described above and a regimen totally 8 infusions.

The clinical program for teprotumumab in thyroid eye disease is the largest clinical program conducted to date in this disease state, and it was designed to answer multiple questions of interest. As is typical with initial registration programs, there are also additional questions that remain and are being evaluated in the ongoing study.

Overall, our approach was informed by discussions with the FDA throughout development, and specific topics discussed included study design endpoints, approach to adequacy of the proposed safety database at the time of BLA submission, and the plan's statistical analyses.

The current FDA draft guidance for rare diseases states that there's a need for a

reasonable number of patients in the safety database, and the overall program size was discussed in this context prior to submission. The safety and efficacy of teprotumumab in thyroid eye disease was evaluated in two well-controlled studies that compared a course of teprotumumab with placebo, which we call study 1 and study 2. All patients in both study 1 and study 2 have completed the 24-week double-masked treatment period.

Both studies contain an off-treatment follow-up period intended to provide information regarding how these patients do in the longer term off therapy. The follow-up off-treatment period of study 1 was for 48 weeks and was designed to look for two things: first, short-term rebound of disease in patients treated with teprotumumab, as this can be seen with steroids; and second, whether response to teprotumumab was maintained a year off of therapy in those patients who had responded to the 24-week course of teprotumumab treatment.

The off-treatment phase of study 1 is complete. Patients will be followed for a longer

period of time off treatment for study 2, and this follow-up period for study 2 remains ongoing. The treatment periods of both study 1 and study 2 together, with the follow-up period of study 1, provide the main demonstration of efficacy and safety that was the basis of our BLA submission.

Additionally, patients from study 1 can be eligible for an extension study referred to as OPTIC-X. We designed a study to evaluate longer durations of therapy, either as continuous after the first 24 weeks or as retreatment. So teprotumumab patients from study 2 who were non-responders at week 24 could continue to receive treatment beyond week 24, or teprotumumab responders at week 24, who subsequently relapsed during the follow-up period, could receive an additional course of teprotumumab.

To increase the number of patients with thyroid eye disease exposed to teprotumumab and to maintain the blind for study 2, entry into OPTIC-X was also allowed for patients who received placebo in study 2. OPTIC-X is ongoing. We have included

available safety data in our briefing book and also in our presentation. Efficacy data will be analyzed and provided once all OPTIC-X patients have completed the treatment period and will give insight into the potential benefit of longer term treatment, as well as retreatment.

In our clinical program, we chose assessments that would evaluate the clinical symptoms of thyroid eye disease that are most important to patients. To speed development, we used tools that had already been developed and were commonly used in clinical studies in patients with thyroid eye disease. Because of their importance to the clinical program, I'm going to take the time to walk through them in detail.

As you heard from Dr. Douglas, proptosis, or bulging of the eyes, is common and impactful. We were in agreement with FDA that this was a critical outcome to assess. There are a variety of ways to measure this. We chose measurement with an exophthalmometer to assess the degree of forward displacement of the eye.

There's literature comparing this to CT scanning, which supports exophthalmometry as a valid and reproducible method that can be implemented across sites for measuring axial globe position. We then took a number of measures to minimize variability in these data. Assessors were all trained as part of study start-up, and the same assessor and same exophthalmometer was used for each assessment of a given patient.

On a population basis, there are race and gender normal values for proptosis. For a given individual, a normal value can only be determined when they are well. Hence, in the clinical studies, we're looking at change from baseline in patients who are categorized as moderate to severe, based on the presence of lid retraction of greater than or equal to 2 millimeters; moderate or severe soft tissue involvement; proptosis greater than or equal to 3 millimeters above normal for race and gender; and/or inconstant or constant diplopia.

Patients were defined as proptosis responders if they had an improvement of at least

2 millimeters. This is in alignment with the guidelines from expert medical and scientific groups in thyroid eye disease and also in agreement with the FDA as per their briefing book, where 2-millimeter change is noted as expected to reduce the incidence of diplopia and improve the lid coverage over the cornea. Diplopia was assessed using a 4-point scale with zero being no diplopia to 3 being constant diplopia.

The inflammatory signs and symptoms of thyroid eye disease, like pain, swelling, and redness, can be very meaningful to patients. These were measured using a tool that has been historically used in clinical studies of patients with thyroid eye disease to catalog the presence or absence of inflammatory signs and symptoms, the Clinical Activity Score, also known as CAS. These three measurements are widely accepted and utilized in clinical studies by the thyroid eye disease medical community.

Lastly, because thyroid eye disease impacts patient's quality of life, including their ability

to function and their appearance, we also included a quality-of-life assessment, the Graves' Ophthalmopathy Quality of Life questionnaire. The GO-QoL is a 16-item questionnaire that is self-administered by the patient and assesses 2 subdomains: functional vision and the impact of appearance on psychosocial functioning.

The questions in the first domain have to do with impact on functional vision, the ability to drive, for example, or read, or walk outdoors. The questions in the second domain have to do with impact on appearance changes and what that can do to have the ability to make friends, for example, or on self-confidence.

This questionnaire was based on those items that are of importance to patients living with thyroid eye disease that are impacted by their disease. The validation was based on literature by Caroline Terwee, et al., as noted in your briefing books, and has been supplemented with content validity with U.S. patients with thyroid eye disease.

Now that I've provided an overview of our clinical program and reviewed the tools utilized to evaluate its efficacy, I would like to turn the lectern over to Dr. Liz Thompson, who will present the clinical data with teprotumumab.

Applicant Presentation - Elizabeth Thompson

DR. THOMPSON: Good morning. I'm Liz Thompson, vice president of clinical development and rare diseases at Horizon Therapeutics. I'm pleased to be here this morning to talk with you about the results of our clinical program of teprotumumab in thyroid eye disease. I'll be starting with the efficacy results and then presenting safety.

In this presentation, I'm going to review the efficacy data from our clinical program. I'll provide data that demonstrate that with 24 weeks of therapy, most patients achieved improvements in proptosis, diplopia, inflammation as assessed by the Clinical Activity Score, and patient assessment of functional vision and appearance.

This program included two studies, study 1

and study 2. These were randomized, double-masked, placebo-controlled trials conducted in the United States and Europe. They were very similar in major design aspects. All patients enrolled were adults with active thyroid eye disease, with onset of symptoms within the last 9 months. Given the potential for embryo fetal harm, based on nonclinical studies, women of childbearing potential were screened for pregnancy and counseled to use appropriate contraception.

In both studies, patients were randomized 1 to 1 to receive placebo or teprotumumab. In both cases, the patient received infusions every 3 weeks for a total of 8 infusions. Efficacy was assessed when the last continuing patient had reached the week 24 visit 3 weeks after the last dose of drug.

Both studies had an off-treatment follow-up period. For study 1, that period is complete, and for study 2, it is currently ongoing. In study 1, the prespecified primary endpoint was a composite endpoint, and we call that overall response. For this, a patient had to have at least 2 millimeters

of improvement in proptosis and at least a 2-point improvement in the Clinical Activity Score.

We did all this in what was called the study eye, which was selected based on being the more severely affected eye. FDA has accepted a single component of that composite, 2 millimeters improvement of proptosis, as the primary endpoint for study 1.

In study 2, we focused on proptosis. To be a responder in study 2, a patient had to have at least 2 millimeters of improvement in proptosis at week 24. We selected this as the endpoint in agreement with FDA and because it's a more objective endpoint. In both studies, for both endpoints, in order to be a responder, the patient couldn't get correspondingly worse in the fellow or less severely affected eye.

Each study was powered for the primary endpoint in that study, with alpha equal to 5 percent two-sided. Study 1 targeted 42 patients per group to achieve 80 percent power to demonstrate a difference in overall response, with

the assumption that overall response rates for placebo would be 30 percent and 60 percent for teprotumumab. In study 2, we targeted 38 patients per group to achieve 90 percent power if the difference in proptosis response was at least 39 percentage points.

Here, I'm showing the list of ranked secondary endpoints for studies 1 and 2. Our goal in this program was to assess the impact across multiple facets of the disease. We have endpoints examining proptosis, double vision, inflammation as measured by the Clinical Activity Score, and the GO-QoL.

In study 1, the endpoints generally examined changes from baseline. In study 2, we added some responder analyses. Of these, the most important was the diplopia responder, which is an improvement of at least one grade; also, the overall response, which again was that study 1 primary endpoint; and those with a clinical activity score of 0 or 1, which indicates no or minimal inflammatory signs or symptoms.

All endpoints, including the primary endpoints for both studies, were met with p-values less than or equal to 0.001, except for the last secondary endpoint in study 1, which was not significant. With that overall summary, I'd like to proceed to a more detailed evaluation of the data. I'll generally be presenting data from studies 1 and 2, next to each other, to provide the full data available on a given topic.

Most patients completed the double-masked treatment period in both studies. In study 1, 88 patients were randomized to either teprotumumab or placebo. One patient did drop out before receiving any study drug. Seventy-six patients, or 86 percent, completed the double-masked period with a similar number completing in both arms. The 5 patients who discontinued teprotumumab during the double-masked period all did so because of adverse events. I'll talk about these in detail during the safety part of the presentation.

Patients who received placebo dropped out for a variety of reasons, including lack of

efficacy, adverse event, and other reasons, which included back surgery, incorrect treatment received, and optic disc edema. In study 2, we had 83 patients randomized, with a total of 79, or 95 percent, of patients completing the double-masked period. Again, the number of dropouts, and in this case the reasons, were balanced across treatment arms with one subject each discontinuing for an adverse event and one for withdrawal of consent.

The demographic characteristics of patients in the trial were generally balanced between placebo and teprotumumab groups in both studies, as well as across studies. The mean age was around 51 years. As we would expect with this disease, the majority of patients were female; also, most patients were white.

On average, patients in the trial had a diagnosis of Graves' disease for about a year and about 6 months since onset of thyroid eye disease symptoms. We saw a higher rate of tobacco users in study 1 compared with study 2. Baseline proptosis was similar across groups and across studies.

Turning now to the results showing that teprotumumab was effective in the treatment of patients with thyroid eye disease, in each of the individual studies, more patients treated with teprotumumab, who are shown in blue, were proptosis responders at week 24 compared with patients who received placebo, who are shown in gray. In study 2, where this was the primary endpoint, there was a 73 percent difference in between treatment groups, and as a reminder, this is the component of the primary endpoint that was accepted by FDA as the primary endpoint of study 1.

An improvement was seen at all study visits. Even at the first post-baseline efficacy measurement at week 6, over half of patients had achieved a proptosis response. Now, the fellow eye was the less severely impacted eye. As one representative example of teprotumumab impact on the fellow eye, here I'm showing the proptosis responder results, and what you see here is even in the less severely impacted fellow eye, we still see improvements in proptosis.

To look at consistency across subgroups, we combined study 1 and 2 data for the study eye, and we found that teprotumumab provided benefit in proptosis across all subgroups at week 24 compared with the placebo group. Teprotumumab was effective in tobacco users and non-users, as well as across patient subgroups by geographic region, age, and gender.

When we look at the degree of proptosis improvement in the individual studies, we see that patients treated with teprotumumab had a greater decrease in proptosis at all study visits compared with patients who received placebo. At week 24, patients receiving teprotumumab had an average proptosis improvement of roughly 3 millimeters in both studies. Averaged across all visits, there was also a significant reduction in mean proptosis that was observed through week 24 in both studies.

On this slide, we show overall response. As noted previously, this was the prepecified primary endpoint for study 1, and as a reminder, this is a composite endpoint that requires a patient to have

both an improvement in 2 millimeters in proptosis and an improvement of at least 2 points in the Clinical Activity Score. This was also a secondary endpoint in study 2. In both studies, a greater proportion of patients treated with teprotumumab were overall responders compared to placebo at week 24 and at all other study visits.

The Clinical Activity Score assesses the presence or absence of signs and symptoms of inflammation, and specifically those are pain, eyelid swelling and redness, conjunctival redness, chemosis, and inflammation of the carbuncle or plica. Our prespecified responder analysis was those with a CAS of 0 or 1, and this means that there was no more than a single inflammatory sign or symptom left after therapy.

In both studies, a greater proportion of patients treated with teprotumumab had achieved this level of CAS response at week 24 and at all other study visits compared with placebo.

As I just reviewed, our prespecified responder analysis reflected those with no more

than a single inflammatory sign or symptom. This analysis does, however, give equal weight to all signs and symptoms. To evaluate a more stringent outcome, which is the complete resolution of those inflammatory signs and symptoms that are assessed by the CAS, we've also performed an analysis of those with a clinical activity score of 0, and roughly one-third of patients treated with teprotumumab achieved complete resolution of the inflammatory signs and symptoms that are assessed by the Clinical Activity Score.

Diplopia, as Dr. Douglas covered in his presentation, can interfere with the ability to perform many everyday activities: driving, reading, holding down a job. Most but not all patients in the teprotumumab studies had at least some degree of diplopia. Of those, a greater proportion of patients treated with teprotumumab saw improvements in double vision at week 24 compared with those receiving placebo.

This was the rate of patients who had improvements in their double vision. Notably, if

you average across both studies, 53 percent of patients treated with teprotumumab had complete resolution of their diplopia at week 24 compared with 25 percent of patients who received placebo. This shows that teprotumumab had a meaningful impact on patients' double vision.

Given the impact of thyroid eye disease on patients' lives, we also assessed quality of life and functioning measurements. We use the Graves' Ophthalmopathy Quality of Life questionnaire to measure changes in quality of life, which I'll call the GO-QoL.

The range of the GO-QoL score is 0 to 100, where higher values correspond to better quality of life. In each of the individual studies, patients treated with teprotumumab had a greater increase from baseline in the GO-QoL at all time points through week 24 than those patients who received placebo; and also, the mean improvements over time were significantly greater with teprotumumab than with placebo.

Now, the GO-QoL questionnaire comprises two

subdomains that assess different facets of the patient experience. These were secondary endpoints in study 1, but given small sample sizes and expected effect sizes, we put these as secondary endpoints for an integrated analysis, which is what I present here.

The first is functional vision. These questions ask about the impact of thyroid eye disease on such activities as reading or driving a car. Here, we see a greater increase from baseline for patients treated with teprotumumab compared with placebo.

A second subscale asks about the psychosocial impact of changes to a patient's appearance. For appearance, patients on teprotumumab similarly reported more improvement compared with those on placebo. And again, I should note that this separation was not statistically significant in study 1, but the integrated analysis shows a meaningful and statistically significant difference between teprotumumab and placebo. Also, the mean

differences in GO-QoL subdomains in the teprotumumab group were each significantly improved compared with the placebo group.

I'll move now from the double-masked period to the off-treatment follow-up. As you heard from Dr. Lin's presentation, this part of study 1 was designed primarily to answer questions about what happens after stopping teprotumumab treatment. The first of these questions was rebound.

As you heard from Dr. Douglas' presentation, cessation of steroids has been known to lead to an acute rebound of inflammatory symptoms in patients with thyroid eye disease. To evaluate whether this was the case with teprotumumab, overall response was assessed at week 28, 7 weeks after the last dose of study drug. It was similar to the week 24 value, indicating no evidence of significant acute disease rebound after cessation of teprotumumab therapy.

The second main question addressed by study 1 off-treatment follow-up was about the persistence of effect in those patients who

responded. To evaluate longer term persistence of effect post-treatment, patients were evaluated at 72 weeks in study 1, which is approximately one year off treatment. Notably, we are continuing to follow patients in study 2.

There are many ways you can think about evaluating longer term maintenance of response, and we'll show a few here. From study 1, there were 30 patients who were proptosis responders at week 24, and these patients were further evaluated for maintenance of proptosis response.

At week 72, approximately a year off drug, 53 percent of patients still had at least a 2-millimeter improvement from baseline, and in total, 73 percent of patients had at least somewhat reduced proptosis from their baseline level and hadn't received any additional treatment like steroids or surgery for their thyroid eye disease. Similarly, of those patients who had a week 24 diplopia response, 69 percent of them were still responders at week 72.

Now, the data package to date gives us

important information about the benefit of a course of teprotumumab, and we do see significant benefit in most patients. In the data we have so far, for those patients who respond to teprotumumab, that response is generally long lasting, with the majority of patients who responded on either proptosis or diplopia continuing to respond after a year off drug.

As you heard from Dr. Douglas and Dr. Lin, teprotumumab treatment may be able to change the course of thyroid eye disease. However, even in therapy that changes disease course may not be curative in all patients, and some individuals may require longer duration or repeat of therapy.

We designed the OPTIC-X study to provide some initial insight into the potential for longer duration dosing, including retreatment, which was not part of the design of study 1. The OPTIC-X study is currently ongoing, and we'll provide efficacy data on continued treatment and retreatment once they're available.

In summary, across two independent and

well-controlled studies, teprotumumab was highly effective and provided clinically meaningful improvements across multiple facets of this disease, including proptosis, diplopia, inflammation, and quality of life, including patients' assessments of the impact on their functional vision and appearance.

For proptosis, this translates to a number needed to treat of 1.6 in studies 1 and 2 combined, which means to get one additional proptosis responder, you would need to treat 1.6 patients. These results were consistent across efficacy endpoints and subpopulations. And importantly, based on what we saw in study 1, the majority of responders were still benefiting from treatment a year after stopping therapy.

We're continuing to explore maintenance in the follow-up of study 2, and we will explore the potential for benefit with retreatment in those patients who don't maintain response, starting with information from our ongoing OPTIC-X study.

Next, I'll review the safety results with

teprotumumab. The safety exposure from our studies in thyroid eye disease includes the double-masked population for study 1 and study 2. The double-masked portion allows comparisons to placebo and gives us a total of 84 patients who were treated with teprotumumab; 43 patients were from study 1 and 41 patients were from study 2.

OPTIC-X is an ongoing study and is still enrolling, so the overall population includes all patients who had enrolled in OPTIC-X at the time that we did our data cut for the 120-day safety update for FDA, and from OPTIC-X, this is 46 patients of whom 37 had received placebo in study 2. When we put it together, the number of patients with thyroid eye disease who'd been treated with teprotumumab is 121, and the overall number of patient-years of exposure is 49.

As you have heard, teprotumumab was initially evaluated in oncology. Looking at that experience, there were 727 patients with 164 patient-years of exposure. Of this, the majority were treated at dosage levels similar to or higher

than that used in the thyroid eye disease population. I'll review the supporting oncology safety profile later in the presentation, but first I'll review the safety profile of teprotumumab in thyroid eye disease.

Most patients in both groups received the full dosing regimen of 8 infusions of study drug. The mean number of days on study drug was similar between the two groups. OPTIC-X is ongoing, and at the time of this data cut, roughly half of the enrolled patients had received 8 infusions.

The majority of patients in both treatment groups experienced at least one adverse event with more patients on teprotumumab experiencing adverse events compared with placebo; and generally, more events were seen in the teprotumumab group across adverse events, leading to discontinuation and serious adverse events compared to placebo.

Events that are serious or led to discontinuation have also occurred in OPTIC-X. Most of these were not considered by the investigator to be related to study drug. I'll go

through these in more detail over the next few slides. I should note that there were no deaths in either treatment group.

Shown here is a list of the adverse events occurring in at least 5 percent of patients in the teprotumumab group in the double-masked population. Muscle spasms were the most commonly reported adverse event in the teprotumumab group. Given their frequency and the imbalancing with placebo, these were identified as adverse events of special interest and will be discussed in the later section. Other commonly reported adverse events were nausea, alopecia, diarrhea, and fatigue. Additional events have been seen in the OPTIC-X study.

Here we've listed the serious adverse events experienced by patients during the double-masked period of studies 1 and 2 and in OPTIC-X. These comprised events that resulted in hospitalization, were life threatening, or were considered by the investigator to potentially require medical or surgical intervention to prevent one of these

outcomes.

There were 3 treatment-related serious adverse events in the teprotumumab group. The first was a patient with a provisional diagnosis of possible Hashimoto's encephalopathy, based on the intermittent fluctuating nature of his symptoms, history of thyroid disease, and a very strong family history of autoimmune thyroid disorder. The second was a patient with an infusion reaction, which also led to discontinuation of study drug, and the third was a patient with diarrhea who had a medical history of colitis.

There were five more serious adverse events that were reported as non-treatment related in the teprotumumab group. The first of these was a patient with a serious adverse event of inflammatory bowel disease, who had signs and symptoms consistent with preexisting IBD. The second was a patient who had a history of HIV and had chills, dehydration, headache, vomiting, and sepsis caused by an E. coli infection. This patient was improved when discharged from the

hospital.

The third was a patient who experienced a serious adverse event of pneumothorax. This patient had medical history, which included throat cancer and radiation treatments, sleep apnea on CPAP, and likely emphysema.

The fourth was a patient experiencing urinary retention shortly after surgery for repair of left inguinal hernia, and the fifth was a patient in OPTIC-X who experienced a cerebral hemorrhage and has recovered. Finally, one placebo patient experienced a serious adverse event. This was a visual field defect requiring emergency optic nerve decompression surgery.

Overall, 7 patients receiving teprotumumab discontinued study drug because of adverse events; 5 patients did so during the double-masked period for study 1 or 2, and two more during OPTIC-X. Patients who discontinued study drug generally did so because of an adverse event that was serious. The only non-serious adverse events that led to discontinuation of teprotumumab were a single case

of muscle spasms and a reaction to pre-medication. I'll describe both of these in more detail in the adverse event of special interest section of the presentation.

In addition to this, one teprotumumab patient was discontinued from study drug due to an adverse event of confusional state that was reported more than 21 days after the last dose of study drug, and this is the same patient who had the provisional Hashimoto's diagnosis.

Infections were more common in the teprotumumab group, however, there was no clear clustering by site or type of infection. The only infection that was serious and led to discontinuation was the E. coli infection detailed earlier and reported as not related.

Further, there was no evidence of opportunistic infections. Infections that occurred in two or more patients are shown here, and what you can see is that these are mostly infections of the respiratory or urinary tract, and all were mild or moderate in intensity.

An important consideration in treatment with biologics is the potential for immunogenicity. In the clinical program for thyroid eye disease, we observed no clinically significant incidence of antidrug antibodies. In study 1, only three samples obtained from two teprotumumab treated patients were confirmed to be antidrug antibody positive. One of these patients was positive at baseline in week 72 and the other was positive only at week 3.

Both patients were negative at all other time points, and their titer levels were 1, indicating very low levels of antidrug antibodies. In study 2, no teprotumumab treated patient was confirmed positive. The assays were designed to have a 1 percent false positive rate.

The presence of these low level, antidrug antibodies did not impact pharmacokinetics, efficacy, or safety. These data are reassuring, especially in the context of potential retreatment with another course of teprotumumab.

I'll next review the adverse events of

special interest. I'll begin with muscle spasms. These were the most commonly reported adverse event in both studies 1 and 2. In the double-masked population, one quarter of patients reported at least one event of muscle spasm, and 41 percent of patients in OPTIC-X have experienced muscle spasms.

Most commonly, this has been described as intermittent cramping. No clinically relevant laboratory abnormalities were observed in these patients. Most have been graded as mild in intensity, with 6 patients experiencing moderate events. To date, all but one of the moderate events has resolved.

The limbs, specifically the lower limbs, are the most commonly affected. No events have involved the maxillofacial area. There's been only one patient to date who has discontinued teprotumumab because of muscle spasms. This patient received placebo in study 2 and reported muscle spasms at that time. Upon entering OPTIC-X, the intensity of those spasms was reported to have worsened, and the patient discontinued the study.

Notably, the patient's CPK was within normal limits.

Next, I'll discuss hyperglycemia, where a higher incidence was seen in patients on teprotumumab compared with placebo. I should note that hyperglycemia is a known class effect of anti-IGF-1R treatments. In the published literature with teprotumumab and other IGF-1R inhibitors, it's generally been reported as mild to moderate intensity adequately controlled by agents for glucose control, and not otherwise interfering with antibody dosing.

In the double-masked population, 10 percent of patients on teprotumumab and 1 percent on placebo reported adverse events of hyperglycemia, and we've also included adverse events of diabetes or increased blood glucose in that number. An additional 3 patients experienced events of hyperglycemia in OPTIC-X.

Per the investigator's assessment of intensity, all of these were mild or moderate. All events were non-serious and didn't lead to

discontinuation, but teprotumumab was held for a single dose in one patient. No patient has been hospitalized or experienced any complication, such as diabetic ketoacidosis or hyperosmolar hyperglycemic state.

Abnormal glucose values were managed in the study with diet and medication, which was most commonly metformin. The highest glucose level in the program was observed in study 1, and that reached 303 milligrams per deciliter on study day 29. This patient had a history of glucose intolerance and had an HbA1c of 7.2 percent at baseline but was not on any anti-diabetic medication. Her second dose of teprotumumab was held, and she was started on metformin but eventually switched to glipizide after which her glucose levels normalized.

The highest HbA1c in a patient with an event of hyperglycemia was 7.9 percent at week 24 in one patient from study 2. This event subsequently resolved off teprotumumab, and the patient was able to discontinue metformin, which had been used to

treat the event.

We would recommend that all patients' glucose be monitored while on teprotumumab. The frequency of that monitoring should be tailored toward the individual's background risk and determined by the treating physician. Let's now look at infusion reactions.

Infusion reactions are common with systemic administration of the monoclonal antibody. In general, reactions may range from mild hypersensitivity to potential anaphylaxis, and therefore monitoring is always required. It's worth noting that while monitoring was implemented in all teprotumumab studies, premedications were not routinely given.

To investigate the potential for infusion reactions with teprotumumab, infusion reaction was considered an adverse event of special interest. The events in this table represent any adverse event that happened in a particular time point. The first is those events that occurred within 2 hours of infusion, and the second line represents

those where the event occurred on the same day, but the onset time was unknown because they could have occurred within 2 hours of the infusion. Of these, 6 teprotumumab events were not consistent with infusion reaction. I'll review the remaining 3 cases in more detail.

The first case comes from study 1. This patient experienced elevated blood pressure and heart rate, rash, and felt hot at the end of the observation period, following the second infusion. Accordingly, she was premedicated before the third infusion and experienced a similar reaction without receiving any teprotumumab. This reaction to premedication led to discontinuation from the study but was considered by the investigator to be unrelated to study drug.

The second case comes from study 2 and was initially reported as an infusion reaction and later updated to hypertension. This is a patient with a history of hypertension who was not taking antihypertensive medication. About 30 minutes after completion of her 5th infusion, this

patient's blood pressure began to rise, continuing to rise for about 1 and a half hours. She was treated and resolved the same day. This patient was premedicated for subsequent infusions, which were also infused at a slower rate, and she was able to complete the treatment period.

The final case was a serious infusion-related reaction in a patient in study 2, which occurred with the first dose. The event was described as an increase in blood pressure and tachycardia; diffuse erythema with facial flushing; increased grandular secretion; a feeling of obstruction in the epiglottis; dyspnea; headache; and muscular pain in the lumbar region and calf muscles.

It was reported that the patient did not experience fever or hypotension. Oxygen saturation was 96 percent. This case met the Sampson criteria for potential anaphylaxis, however, the investigator did not consider the event to be anaphylaxis and did not treat it as such. The infusion was stopped.

The event was treated with IV steroids and antihistamines but not epinephrine. The event was noted as resolved approximately 2 hours after onset. Approximately 3 and a half hours post-dose, serum tryptase levels were normal. The patient withdrew from the study and was not rechallenged with study drug.

In all of these cases, patients were managed with symptomatic treatment and all resolved the same day without sequelae. One patient was able to receive the rest of the doses of study drug using premedication and a slower infusion rate. No patient received epinephrine.

Let's now look at hearing impairment. Literature suggests a 14 times increase in hearing impairment related to a diagnosis of Graves' disease. That said, there is an imbalance relative to placebo. The term "hearing impairment" here comprises a broad range of terms such as eustachian tube dysfunction, tinnitus, and deafness.

In the double-masked population, 8 patients treated with teprotumumab experienced events of

hearing impairment. Specifically, this included 3 cases from study 1. One patient has resolved, one was improving on last contact, and the third was noted as ongoing in a patient who had preexisting tinnitus related to loud-noise exposure. All cases in study 2 have resolved.

An additional 5 patients in OPTIC-X, who are ongoing in the study, have experienced events of hearing impairment. All of these have been graded as mild, and three have either fully or partially resolved to date, and the others are ongoing in the study.

All events were non-serious and were graded as mild or moderate in intensity. To date, the majority have resolved or improved, and most others are in an ongoing follow-up. Of the 13 patients with hearing impairment, 8 underwent audiology testing by judgment of the investigator, including all patients with events that the investigator considered to be of moderate intensity, and let's look at these in more detail.

The majority of patients' audiograms

revealed mild to moderate sensory neural hearing loss. The events of hearing impairments seen with teprotumumab do not appear progressive. There were 2 cases that were unilateral. While it's not definitive, it is unlikely that this is associated with ototoxicity from a systemically administered agent.

Four patients exhibited high frequency hearing loss. Ototoxicity typically begins in the frequencies above 8,000 hertz and later affects lower frequencies; however, this is also the pattern associated with age-related hearing loss. Although these data are confounded by hearing impairment that is associated with Graves' disease and advancing age, there is a clear numerical imbalance in the teprotumumab group relative to placebo.

Now, let's look at inflammatory bowel disease or IBD. In study 1, 2 patients experienced serious events related to inflammatory bowel disease. One was a serious adverse event of IBD exacerbation and the other was a serious adverse

event of diarrhea. The first patient had underlying inflammatory bowel disease and the second had signs and symptoms consistent with underlying disease.

As a precaution, we decided to exclude patients from study 2 with a history of inflammatory bowel disease. We also selected diarrhea as an event of interest for the study 2 population to monitor for potential new onset cases of inflammatory bowel disease.

In the study 2 population, events of diarrhea were balanced between treatment arms. All events were mild or moderate and did not lead to study drug discontinuation. We also looked at terms related to abdominal pain or bleeding, and this was also balanced. No events of new onset IBD were observed.

Overall, teprotumumab was generally well tolerated with manageable adverse events. Adverse events, as well as serious adverse events, and adverse events leading to discontinuation, were more common with teprotumumab than with placebo.

Most of these events were mild or moderate and resolved either during or after treatment.

Eighty-nine percent of patients were able to receive all 8 infusions of teprotumumab in studies 1 and 2. No significant shifts in laboratory findings were noted, with the exception, of course, of the elevated glucose and hemoglobin A1c levels in some patients. There were no clinically significant changes in vital signs or ECGs, and the only antidrug antibodies detected were transient, low titer, and observed only in 2 patients.

I'll now review the oncology experience that supports the safety profile of teprotumumab in thyroid eye disease. As a reminder, there were nine studies conducted in oncology with teprotumumab. I'll focus on two studies, which represent more than half of the patients and most of the exposure to teprotumumab in oncology. It's important to keep in mind, however, that these studies represent very different patient populations. These patients have late-stage cancer, have generally received prior cytotoxic

medication, and, at least in the non-small cell lung cancer study I'll show you, are also receiving concomitant oncology treatment.

It's important to note further that patients who died due to disease progression for their underlying malignancy are not included in these following SAE tables in order to better determine causality due to teprotumumab. Our approach to the oncology data was to evaluate for commonality with thyroid eye disease. I'll start with the serious adverse event data in advanced non-small cell lung cancer.

The advanced non-small cell lung cancer study is the only placebo-controlled study with teprotumumab in oncology. It was conducted on a background of erlotinib. Although there's no consistent pattern of serious adverse events, there are some numeric imbalances relative to placebo, and although these numbers are small, there are a few categories that appear consistent with the thyroid eye disease safety experience, including infections, GI disorders, and metabolism.

Next, I'll show the adverse events for the patients on teprotumumab non-small cell lung cancer. Rash is the most common adverse event seen in this study. It is a known side effect of erlotinib, which was received by all patients in this study. Other common events such as diarrhea, fatigue, and nausea are also part of the known safety profile of erlotinib and have been observed to a lesser extent in the thyroid eye disease program.

Muscle spasms were common in thyroid eye disease and are seen here as well. And also consistent with what we saw in thyroid eye disease patients and what we know about the class of IGF-1R inhibitors, hyperglycemia was reported in these oncology patients.

I'll now move to the refractory sarcoma study to add some additional detail. The study in refractory sarcoma is the largest monotherapy study run with teprotumumab in oncology. Few serious adverse events were experienced by more than one patient. Although it can be argued that infection,

pneumonia, and device-related infection represent a higher frequency of infections when grouped together, the details of these events suggest no specific pattern to organ type or type of infection, and they did not include opportunistic infections.

Again, the numbers are small, and a lack of a control arm makes it difficult to draw firm conclusions in this late-stage oncology population. Let me now look at the adverse events in this study.

Most of these adverse events are consistent with underlying late-stage malignancy. The most common preferred terms are fatigue, nausea, and diarrhea. These were seen to a lesser extent in thyroid eye disease. Again, hyperglycemia was common here, as were muscle spasms. In addition, infusion-related reactions were also observed.

Overall, most of the elements of the safety profile described for thyroid eye disease are seen consistently within the oncology safety database. That said, we acknowledge the challenges of

cross-indication comparisons, and as such, we are proposing a postmarketing plan to continue to educate physicians and patients and ensure appropriate use of teprotumumab in thyroid eye disease.

Our proposed postmarketing safety plan consists of four cornerstones: enhanced surveillance, labeling and education, and support for healthcare providers and patients. We're also proposing a registry following approximately 200 patients and plan to discuss this and finalize with the FDA.

With pharmacovigilance, we'll proactively follow up on adverse events of special interest such as hyperglycemia, muscle spasms, and hearing impairment. For the teprotumumab label, we'll work with the FDA to inform the prescriber and HCP community to ensure safe use. For healthcare providers, we'll have a call center focused on healthcare professional questions and are committed to continue to communicate teprotumumab data through peer-reviewed publications.

For the patients, Horizon is creating a network of call centers staffed by pharmacists and nurses to provide teprotumumab information to patients at every step of their journey, with an additional line to provide support for patients who are receiving their drug through a specialty pharmacy. And lastly, Horizon will partner with several advocacy organizations to distribute educational materials to patients and caregivers on the risks and benefits of teprotumumab.

Now, having reviewed both the efficacy and safety results from our clinical program, I'd like to summarize the benefit-risk profile in thyroid eye disease.

Thyroid eye disease is a progressive autoimmune disease. Sight impairment from optic nerve compression or severe corneal exposure occurs in roughly 6 percent of patients with thyroid eye disease, but the threat to functional vision is much more common. Double vision can interfere with many activities of daily living such as reading, walking, or driving a car, as well as the ability

to work. There are no FDA-approved therapies for this disease, and the existing treatments don't impact proptosis or double vision.

The data support that teprotumumab delivers important benefits. Teprotumumab produced statistically significant and clinically relevant improvements for patients suffering from proptosis, diplopia, and inflammation. Finally, we saw a meaningful improvement in patient's quality of life with their own assessments of their functional vision and their appearance improving.

The study of teprotumumab has also identified risks. The risks of hyperglycemia, infections, and infusion reactions have been noted. Hearing impairment has been reported in some patients. To date, these events have been mild or moderate in intensity and have resolved or improved in most patients. Muscle spasms are commonly experienced but generally have been graded as mild.

It may be appropriate to exercise caution when treating patients with preexisting inflammatory bowel disease. And finally, based on

findings in animals and its mechanism of action, teprotumumab may cause fetal harm if administered to a pregnant woman. Contraception was required in the clinical program, and no pregnancies have occurred. Each of these risks is included in our proposed label.

Overall, the data show that the benefits of teprotumumab outweigh the risks observed in patients with thyroid eye disease, a progressive, vision-threatening, rare auto immune disease. Thank you. I'd now like to ask Dr. Douglas back to the lectern to talk about his clinical experience with teprotumumab.

Applicant Presentation - Raymond Douglas

DR. DOUGLAS: Thank you, Dr. Thompson.

As someone who has enrolled 22 patients to date, including retreatment of one, I'd like to put the data that you just heard into a clinical perspective. Each of my patients expressed how the treatment was incredibly impactful to their lives. Each expressed how it restored their function and appearance.

First, as I discussed earlier, thyroid eye disease is a severe and debilitating disease that negatively affects patients clinically, physically, and psychologically. Patients constantly express how the impact of this disease is often overlooked or underestimated by others, but the reality is that this disease affects all aspects of their lives.

On the exterior, everyone sees how patients suffer from obvious bulging eyes, however, most patients also suffer every day and every hour with vision problems. Strabismus, double vision, blurry vision, and red painful eyes plague my patients every day. They wake up with the problem, often in intense pain despite wearing eye masks and Saran wrap to keep their eyes shut. They deal with their disease every hour trying to drive, trying to use a computer, and all the while in discomfort and having distorted vision. Additionally, they have permanent facial disfigurement and social isolation.

As I mentioned earlier, there are no

approved treatments for thyroid eye disease. Simply put, the options that physicians like myself are left with provide patients little benefit as they do not address proptosis or double vision. Instead, therapies such as high-dose glucocorticoids present enormous challenges. Personally, I discourage use of high-dose group corticoids because of their substantial side effects and no long-term benefit. For most of my patients, we wait for the disease to stabilize. Frankly put, my patients are frustrated and want anything that will help improve things for them.

As the principal investigator for the teprotumumab clinical program and someone who regularly sees these patients, I can tell you that teprotumumab has the potential to reverse this disease and significantly improve the lives of patients inflicted with it. The lives of the patients I treated with teprotumumab in the trial were transformed for the better. Let me show you some patient examples from the study.

In the top row, you see the patients at

their baseline with a placebo patient in the gray on the far left and two teprotumumab patients in blue, one in the middle and one on the far right. As you can see, teprotumumab visibly improved the two patients to the right, which is representative of what I have observed in the clinical studies. Both the placebo patient and the first teprotumumab shown suffered from extensive proptosis.

Let me walk you through each of these cases in more detail. After completing 24 weeks of treatment in the placebo arm of the study, you can clearly see the natural history of this disease. As is typical, after 24 weeks, the placebo patient did not demonstrate any improvement in the disease state.

The first teprotumumab patient shown here has a story that is typical of so many of my patients. He's a restaurant owner but also works a second job at night to make ends meet. He developed thyroid eye disease, which completely devastated his life. He no longer could drive to work and couldn't bear the pain, discomfort, and

vision changes to keep his restaurant operating. Without definitive treatment, he was planning to sell his restaurant since he could no longer manage it. He enrolled in the trial, and within 2 doses of teprotumumab had significant improvement.

In the photo, we can see his improvement over the course of treatment. It was so dramatic that he was able to continue working and was able to maintain his restaurant. Even though his case was severe, this typifies how thrilled my patients were to regain their lives after treatment.

This patient from northern California noticed his bulging eyes. He was frustrated by the excessive tearing and light sensitivity. He had a job that required him to be outside driving. Sunglasses helped, but he still had issues conducting his job. With teprotumumab treatment, he experienced an improvement in proptosis, and he's now back at work functioning well.

These examples are well representative of the life-altering effects of thyroid eye disease. These patients struggle day to day. The treated

patients also demonstrate significant improvement patients had after teprotumumab and the ability to regain their lives. As dramatic as these clinical photos are, the changes occurring behind the eye in the orbit are the most impressive.

I perform MRIs on most of my patients as part of their usual medical care. The left image shows a coronal MRI, typical of moderate to severe thyroid eye disease. There's inflammation and increased size of the extraocular muscles. There's also inflammation within the orbital fat compartment, and both are indicated by the white arrows.

On the right image, after treatment, there is substantial reduction in the inflammation of the orbital muscles and fat as seen by normalization of the signal in these structures. The marked reduction in both muscle and fat is shown by the white arrows.

For clinicians such as myself who treat thyroid eye disease routinely, it is unprecedented to see this type of improvement, particularly in

extraocular muscle size. Overall, there are three things that are most impressive to me about teprotumumab.

The first is its rapid onset. Patients experienced visible improvement at the first assessment at 6 weeks, and patients continued to improve throughout the 24-week period. The second most impressive thing is its depth of effect. This is also most impactful to patients to see their disease melting away.

The results with teprotumumab were similar to what I can achieve with surgery, however, with the surgery, I must wait many months or years for the disease to stabilize, and then subject patients to a surgery where I drill the bone behind their eyes, often requiring multiple surgeries separated by months. This depth of effect with teprotumumab was approximately what would otherwise be achieved with surgery without surgical complications, showing teprotumumab alters the natural history of thyroid eye disease.

Third, teprotumumab achieved these results

with a favorable safety profile. Patients tolerated teprotumumab well with few discontinuations. None of my patients ever thought about stopping the treatment; in fact, my patients were very pleased with their treatment outcome.

The totality of the evidence shows that teprotumumab offers patients and healthcare professionals the first highly effective and generally well tolerated treatment for thyroid eye disease, a devastating rare and vision-threatening disease for which there are no approved therapies. A single course provided meaningful improvements, and for many responders, it led to prolonged response off drug.

From my perspective, as someone who manages these patients on a daily basis, teprotumumab is an appropriate first-line therapy for the treatment of thyroid eye disease, as it has the potential to be disease modifying. My colleagues and I are excited about the opportunity to hopefully offer this treatment to our patients in the near future.

For the first time, we have an opportunity

to use a medical therapy that reverses the disease to substantially impact the disease process and patients' lives. Thank you. Dr. Thompson will now return to moderate the question and answer session.

Clarifying Questions to Applicant

DR. CHODOSH: Dr. Burman, will you come to the podium?

DR. BURMAN: Ken Burman. I have three clarifying questions. The first are Dr. Douglas very nicely showed -- in fact, the whole presentation was nice, but Dr. Douglas very nicely showed the benefits of doing an MRI or CT scan, and I wonder why they weren't performed in the study, study 1 and study 2, when it would have been so much more quantitative for proptosis and retro-orbital effects.

Question number 2 is you didn't show any data regarding treatment for hyperthyroidism nor thyroid function tests either before or during the treatment. And number 3, although it's less important, any effect on growth hormone, it should be lower, and I wondered if that had some benefit

as well. Thank you.

DR. THOMPSON: I'll address the first two of those questions, and then I'll ask my colleague, Dr. Ramanathan, to come up and talk about the growth hormone piece.

With respect to the choice to not include CT or MRI in these studies, proptosis, measured using an exophthalmometer, has been found to be a reproducible and valid method of estimating axial globe position across sites, and that was actually done in a study where it was compared to CT scan. We picked this based on the fact that it's an efficient way for us to evaluate teprotumumab's impact on thyroid eye disease.

We certainly agree that the results of Dr. Douglas' scans are very interesting, and we're very pleased that he did them, but the proptosis was able to be reliably and adequately measured across sites with the exophthalmometer, so that's what we pursued at the time.

With respect to data on thyroid function, what we did see was that there was no meaningful

impact. Actually, I can bring up a slide to show you; that there's no meaningful impact on TSH levels throughout the course of the studies, with either teprotumumab or placebo; so this seems to stay steady throughout.

Dr. Ramanathan?

DR. RAMANATHAN: Srini Ramanathan, development sciences, Horizon Therapeutics. We did not measure the levels of growth hormone in our studies, but the early studies that were done with teprotumumab did evaluate levels of IGF-1, and they were increased.

DR. BURMAN: Ken Burman. I'm sorry; a real quick follow-up. How were the patients treated for their hyperthyroidism at the outset, and how many were you tie euthyroid?

DR. THOMPSON: We did ask that everyone within the study be euthyroid, but the definition of euthyroid was within 50 percent of normal limits. In terms of the medications that were used to treat thyroid disease, they were primarily either sulfur-containing imidazole or thyroid

hormones.

DR. CHODOSH: I have two questions, but I'd like to ask them separately. We heard today from Dr. Douglas that radioactive iodine can exacerbate thyroid eye disease. In the U.S., it's been my experience that the majority of patients who are diagnosed with Graves' disease are sent immediately for a radioactive iodine treatment, often immediately upon diagnosis; whereas in Europe, I know that's less commonly done.

The question I have is whether the patients in this study had been treated with radioactive iodine and whether that might have some effect on the outcome and use of this particular agent.

DR. THOMPSON: We did have a -- well, I don't know if I should say it's relatively low. Ten percent of patients in both treatment groups had a history of radio-iodine therapy. It was balanced across.

DR. CHODOSH: Was there any suggestion of a difference in response? We know that some patients have thyroidectomy done in Graves' disease. It's a

minority of the time, but it's done by some practitioners who believe that it's protective against thyroid eye disease; again, without hard data, in my view. But was there any suggestion of a difference in treatment effect as to how Graves' disease was initially managed in these patients?

DR. THOMPSON: We don't have that analysis available on a slide right now. I'll get my backroom working on it, and we'll try to provide those data after the break.

DR. CHODOSH: Dr. Brittain?

DR. BRITTAIN: It's Brittain, actually.

I have a couple of questions, first about safety, and then a quick question about efficacy. I'm trying to get a context for the size of the safety database. First of all, I'm not quite sure how rare the disease is. I'm not sure we actually heard any numbers about that.

I also was wondering did the FDA agree that this size study was adequate. I know you mentioned that there were discussions, but I wasn't clear that there was an actual agreement that this size

database was adequate. Also, it would be useful to show confidence intervals for the relative risk of the various adverse events we saw. I assume you've done those. Also, I agree that it was a nice presentation.

DR. THOMPSON: Thank you. There were a few pieces there. I'm hoping that I've noted them all down, but feel free to remind me if there's something that I've missed in there.

So the incidence of thyroid eye disease, there aren't great epidemiological data as is often the case with rare diseases. What we do know from the published literature and what we've been able to estimate with the current U.S. population is that annual incidence is less than 25,000 patients per year, with an expected overall prevalence around 75,000 patients per year -- or sorry; 75,000 patients total for prevalence.

With respect to the question about the agreement on the safety database -- and I certainly invite Dr. Chambers to correct me if I say anything that he thinks is not an accurate

representation -- at our pre-BLA meeting, the assessment of the FDA was that the efficacy and safety appeared adequate but was going to be a subject to review. So I think that's probably the best comment I can make there.

DR. CHAMBERS: Wiley Chambers. There is no minimum requirement for the submission of either a new drug application or biologic license application. The expectation is that you will have at least two adequate and well-controlled trials, and this application clearly meets that.

DR. BRITTAIN: I'm sorry. I did ask about confidence intervals --

DR. THOMPSON: Yes.

DR. BRITTAIN: -- and maybe I'll also ask my other question, which I think will be quick. You have very clear-cut results on efficacy, but it wasn't clear to me how you were handling the missing data. For example, the people who discontinued, were they measured at 24 weeks, and if not, how did you handle them in the analysis?

DR. THOMPSON: So with respect to the

question on confidence intervals on safety, if we can look for that. With regard to the question about handling of missing data, I can ask my colleague Dr. Wiens to come up and address that.

DR. WIENS: Brian Wiens, vice president of biometrics, Horizon Therapeutics. Subjects who discontinued therapy were invited to return at week 24 for the efficacy assessment. As is often the case, very few did. So if the efficacy assessment was missing at week 24, for the primary endpoint, which was dichotomous, we imputed non-response for those subjects. If the subject had discontinued therapy and did show up, we took whatever measurement was obtained.

DR. CHODOSH: Dr. Harnett?

DR. HARTNETT: Thank you for a very informative presentation. I have a few questions around dosing, and then just a general question about whether or not you looked at -- I'll ask that first.

Is there a concern about insulin resistance being increased over time? Because it was

mentioned that the thinking behind the hyperglycemia was due to increased gluconeogenesis, and if that might be considered something to look for in the future.

DR. THOMPSON: I'll ask Dr. Ramanathan to get up and talk a little bit about what we understand about the mechanism of impact on glucose.

DR. RAMANATHAN: Srini Ramanathan. The mechanism that drives the increase in hyperglycemia is essentially the dysregulation of the negative feedback inhibition of IGF-1, which then drives growth hormone production. I can show you this using this cartoon that we have, or a schema.

Normally, you have IGF-1 production from the liver that entails stimulation by growth hormone. In general, IGF-1 negatively regulates growth hormone secretion by the pituitary. On the other hand, when you have IGF-1R blockade, what you see here is an increase in growth hormone production, which then has an increase in glucose production. In order to compensate for that, there is an

increase in insulin production.

So this normally is managed in patients who have intact insulin function, and for those who can't, there is a slight increase in glucose.

DR. HARTNETT: So as a follow-up, will you be looking for increased insulin? That is considered -- or is being looked at as concerns with some age-related diseases.

DR. THOMPSON: I'm sorry. I'm not sure I heard the question. Would you mind repeating it?

DR. HARTNETT: Yes. So hyperinsulinemia is being considered a concern in some age-related diseases, and I was just wondering if that was on your radar moving forward.

DR. THOMPSON: Certainly, both in our pharmacovigilance, as well as in our proposed registry, we would be continuing to look at hyperglycemia and related events. So this is something that we recognize is clearly a mechanistically related event of the drug, and we'll keep an eye on it.

DR. HARTNETT: I just had a few questions

clarifying about dose. Are there any data just for considering not having a total of 8 infusions in some patients if they start to show a response? In other words, the recurrence rate, are you concerned that you'll have more recurrences, or do you think some patients who are showing a very good response without the full 8 infusions might have fewer?

DR. THOMPSON: It's an interesting question, and I don't have clinical data that directly can address it because what we studied was that 8-infusion course, and the maintenance, the response, after the 8-infusion course.

Certainly at a population level, it does appear that we're getting to a plateau of response only at the very end of the dosing period, suggesting that this 8-infusion treatment course is necessary for patients to get their maximal benefit. One could postulate, and I would postulate, that perhaps with fewer infusions, you might be less likely to maintain a response, but we have no clinical data to address that.

DR. HARTNETT: Thank you. Also, about side

effects, adverse events, does it seem that more infusions increase that risk? When you said that patients, for example, with spasms had resolution, was that right after the infusion or were the spasms --

DR. THOMPSON: So in some patients, those spasms were really described as intermittent and would sort of come and go. So for some of those, the adverse event was quite long in duration, representing something that just came and went during that course.

With respect to your question about whether fewer infusions might lead to fewer adverse events, we did see adverse events that occurred throughout the treatment period. There wasn't any obvious suggestion that more infusions were correlating with an increase in adverse events later on in the treatment period. So our estimate is that this treatment course provides maximal benefit and doesn't seem to provide substantial additional risk.

DR. CHODOSH: I had a follow-up question

from Dr. Hartnett's question, which is really similar. Now you've got this third study ongoing, and some of the patients have had quite a few infusions I would imagine over time.

The question, again, was have you seen any suggestion of adverse events occurring with time and infusion number? Because you have a rate in each of the two studies, and then presumably you're generating a rate in your -- is it OPTIC-X --

DR. THOMPSON: Yes.

DR. CHODOSH: -- study, and there are patients, for example, that had no muscle spasms in the treatment arm of the first study, but then went into OPTIC-X because they had a regression of effect.

Are they then having muscle spasms when they didn't have it before? That gets back to Dr. Hartnett's question of to what degree are these various side effects additive over time and infusion? I think this is important because it's not yet established, at least in my mind, what is the optimal treatment duration, and I think you're

getting at that with your OPTIC-X.

DR. THOMPSON: We are trying to explore that. I have to put the caveat that, at this point, the number of patients who received teprotumumab in study 2 and have received teprotumumab in OPTIC-X are very small. That's 9 patients total at this point. Five of them went directly into OPTIC-X after completing study 2, and the other four are retreated. So this is a very minimal data set that I can address here.

In terms of the kinds of adverse events that have been seen in these patients, they are consistent with the adverse events that we saw initially. What I'll have to get back to you on is we do have a couple of patients who have experienced muscle spasms. I'll get back to you on whether they had also experienced muscle spasms in study 1 -- or study 2; sorry.

DR. CHODOSH: Dr. Wang?

DR. LOW WANG: Cecilia Low Wang. Thank you also for that great presentation. I thought that was very informative. In terms of safety concerns,

I think the short-term risks, to me, seem to be the highest with muscle spasms and hearing loss, but I'm really concerned about long-term effects and just the inadequacy of the safety database.

We have about 213 patient-years of follow-up, total, for teprotumumab, and I think that the implications of long-term hyperinsulinemia can't be detected in a short time; development of metabolic syndrome; risk for cardiovascular disease; and then later on, also potential risk for different malignancies with elevation of growth hormone.

Could you comment on that?

DR. THOMPSON: I think what I'll comment on primarily at this point is acknowledging the long-term safety that we have. It's relatively limited in terms of longer term treatment. In fact, mainly what we have is a few patients from the long-term oncology studies, but that's really limited in what it can tell you.

That said, for the majority of patients, 6 months and then going off of treatment worked

well for them. We're not envisioning that this is a therapy that's going to be chronic therapy for everybody. We are investigating what happens with longer term therapy and what happens with retreatment, but we would not envision that this would be a chronic, life-long therapy for patients.

DR. YOO: Dave Yoo. Thank you for an amazing presentation across the board. The one thing that I wanted to ask was for the proptosis with the teprotumumab, looking at tobacco users versus non tobacco users; two questions. The first question is, diplopia also improved with those groups, with the tobacco group, as well as the quality of life? And then secondly, for those people that have been using tobacco in the study, looking after the treatment, have you noticed a prolonged effect, continued effect, of the proptosis reduction and those other measures as well?

DR. THOMPSON: We should be able to pull up our pooled data looking at tobacco users and non-users on diplopia. Keep in mind, we're getting

to smaller and smaller subgroups here. We're looking at just those patients who have diplopia and just those patients who are tobacco users. You see numerical separations in both cases.

Then I think you'd also ask about quality of life. Can we get the quality-of-life pooled? Sorry. I should've been more clear; quality of life pooled in tobacco users. Bear with me for a moment.

So what you see here is the quality of life by tobacco users on the left-hand side, non-users on the right-hand side, and again, clear numerical separations, and again, a smaller number of patients. Here, we've got a little bit more than the prior one because everybody was evaluated for their quality of life rather than not everyone having diplopia.

DR. CHODOSH: Thank you. Dr. Murray?

DR. MURRAY: I had one comment and two questions. First of all, excellent presentation.

DR. THOMPSON: Thank you.

DR. MURRAY: The study design was really

well developed, but I think it is bothersome to many of us that it is such a few number of patients in totality that have been evaluated in the two clinical trials. For many of us, that number is really quite small compared to other data sets that we've evaluated. So I think I'd love a context from you just as to how comfortable you are with numbers when you're looking at potential long-term impacts in such small sample sizes.

In your group, you had a 75 percent response rate, which is amazing. Were you able to predict in that subset of patients that were non-responders; is there any clue as to early analysis as to who may be a failure to respond so that they could drop off study drug early?

Then number 3, often when a drug's approved, we find its uses beyond its label in many instances. How are you going to focus on what active disease in terms of a proptotic patient with thyroid eye disease versus a patient that may be inactive with proptosis?

DR. THOMPSON: So taking the size of the

safety database first -- and again, please feel free to remind me if there are questions that I don't get to at the end -- we do acknowledge that this is a small safety database. This is a rare disease, and that is often the case there. This is the largest clinical program that has been run in thyroid eye disease, and we consider that the safety population is reasonable size, but of course that is somewhat in the eye of the beholder.

We are committed to continuing to explore the safety profile of this, and that is why we're proposing a registry where we would collect information on 200 additional subjects. We do find the oncology supportive data to be supportive. There are many caveats you need to apply to it, of course, but it is a large number of patients treated for similar periods of time at similar doses, and we're not seeing safety profiles out of that population that are not either consistent with the disease background or similar to what we're seeing in thyroid eye disease.

As far as the question about predictors of

response, the challenge -- and this is a challenge that is very nice to have -- is when you have such a high rate of responses, you have relatively few non-responders to look at. So we've not found consistent predictors of response or non-response. We did actually do a systematic CARD analysis to try to find something, and we weren't able to. It could just be because we have so few non-responders at this point, we can't find the defining factor, or it may be that there really isn't one

I think there was a third question, and I didn't jot it down. I apologize.

DR. MURRAY: I think the indication for active disease as a treatment indicator.

DR. THOMPSON: As I think you'll see from the questions from FDA, certainly I think part of what we need to discuss here today is about the utility of active as telling physicians how to treat. We will of course do any of our promotional efforts, or whatever, within the context of whatever that label may eventually be. I'll say that in our study, what we looked at was active

patients based on the number of inflammatory signs and symptoms that they had. So that's what we studied, and that's our best current clinical data to address what active is.

DR. CHODOSH: I have a follow-up on that, and then we're going to take a break. The inclusion criteria said active disease within 9 months of onset, then, again, you have this OPTIC-X study and you're looking at response. Is there any indication of reduced response with time from onset? Because we would predict that from the natural history of disease, but the farther out you get from the onset, the more fibrosis you get, the less you're going to respond to an agent like this.

So is there anything in your data to be consistent with an impact from time to onset that might be helpful and instructive to this definition of what is active disease? Because if I'm a patient with thyroid eye disease, it never stops being active because it's never fully treated, at least in my experience; that these patients never are really satisfied with their visual function,

appearance, et cetera, ever, at least with current therapy.

DR. THOMPSON: I have limited information that I can provide on that, and then I'll ask Dr. Douglas to come up and comment on his thoughts.

First, I'll comment that we did look at predictors of response and didn't find duration of thyroid eye disease to be one of those in the context that we had to have everybody within 9 months of diagnosis. So that gives you a little bit of information but not complete information to answer your question.

The other thing that you could keep in mind is that there's the duration since onset that can be a way of thinking about activity, and also the amount of inflammation is another way you can think about activity. In our patients, they did have to have a certain number of inflammatory signs and symptoms in their study eye. We did have some patients with fellow eyes that were less inflammatory.

In that small number of patients, where they

had a clinical score of 2 or lower, we still saw 58 percent of them having a proptosis response, suggesting that even in patients who are less inflamed, they still can get benefit of teprotumumab. This is very limited, but it's within the context of the data I have.

I'll ask Dr. Douglas to get up and comment on his thoughts about activity and inactivity.

DR. DOUGLAS: Disease activity is often difficult, even for us clinical practitioners, to define, but we often look at it and we've worked very hard in trying to categorize it in two main ways. One is through the Clinical Activity Score, which primarily measures the degree of inflammation, and the other is through progression of disease, or disease that's changing over time. So both of these are usually helpful in thinking of active disease and what may be defined as active disease.

I also want to point out that our studies have demonstrated an overexpression of the IGF-1 receptor in biopsy tissues that were largely even

from stable phase disease. So the biologic process of overexpression of the IGF-R also appears to be in those tissues as well, as were the initial studies. So I think, at this point, I often think of the risk and benefit associated with this drug and that we really don't have any great treatments to offer these patients that don't carry significant side effects. So I think all of those things will be taken into consideration in thinking of patient care.

DR. CHODOSH: Thank you. I think the critical thing here in my personal view is if this agent were approved, patients who are not going to respond not be unnecessarily treated because there are side effects associated with the drug, at least based on the data that we have.

DR. DOUGLAS: There is likely a point where this disease becomes fibrotic and irreversible. It's just that these are quite dynamic and hard to know on an individual basis.

DR. CHODOSH: Thank you.

We're going to take a break now for 15

minutes. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience, and we're going to reconvene at 10:20 a.m. For those panel members still hoping to ask questions, we have you on our list, and we'll get to them in the next bit. Thank you.

(Whereupon, at 10:05 a.m., a recess was taken.)

DR. CHODOSH: We're going to get started again. This meeting is back in order. If Dr. Weng would ask her question, please?

DR. WENG: Thank you very much for the introductory presentations. I just have two quick questions. The first is regarding the hearing-related adverse effects that were noted in approximately 10 percent of the study patients.

You showed us, Dr. Thompson, some of the adverse effects from the nine other oncology studies, but I didn't notice any hearing loss or tinnitus-related adverse events in those studies. Were those looked at, and were the proportions

similar?

My second question is in regard to the efficacy and outcomes here with teprotumumab. Were the outcomes stratified by initial CAS? For instance, if someone was more severe coming into the study, was that reflected in the amount of decrease in CAS or proptosis that was observed?

DR. THOMPSON: With respect to hearing in oncology, in 6 of 9 studies -- and actually I'll just project this -- there were adverse events of hearing impairment that were reported. These were generally actually at lower rates. Only one of the studies has a rate of 13 percent. In the other three studies, there were no hearing impairment events noted.

The caveat here is, of course, the fact that these patients have generally -- most of them have received prior chemotherapies, including platinum-based chemotherapy; so the nature of hearing impairment in these patients is a little difficult to understand, but it is here, though, at lower rates.

With respect to the question about Clinical Activity Score and whether it was taken into account for the analyses, that was actually not accounted for in the analyses. We did adjust the continuous variables for a number of different factors, but baseline Clinical Activity Score was not one of them.

DR. CHODOSH: Dr. Hartnett?

DR. HARTNETT: Thank you. With regard to teprotumumab causing reduction in IGF-1R expression in target tissues, is there a possibility that the drug is actually changing the natural history? This is in regards to follow-up from Dr. Chodosh's question about activity level. Did you look at serum biomarkers? Is that a possibility? Because there may be a potential that the drug actually changes the course from what we know the natural history to be.

DR. THOMPSON: I'll ask Dr. Ramanathan to come up and comment on our thoughts on disease modification, and then potentially ask Dr. Douglas to add some commentary.

DR. RAMANATHAN: Based on its mechanism of action, teprotumumab could biologically be plausible to modify the course of the disease. As you heard in Dr. Lin's presentation and as reiterated by Dr. Douglas, the orbital fibroblasts were obtained, where a lot of the active teprotumumab was demonstrated in terms of driving the key pieces of the pathogenesis of the disease.

The cytokine-driven immune infiltration, the extracellular matrix deposition, adipogenesis, a lot of these actually were, in fact, obtained from patients who had undergone surgery. They are naturally getting to that part of their disease phase where their inflammatory symptoms are subsiding, and it's primarily the proptotic events that are continuing to manifest.

So in a setting like that, we have been able to demonstrate that there is a reduction of the pathogenic driver, so biologically, it is plausible that teprotumumab could be active in a wide spectrum of the disease phases.

I'll invite Dr. Douglas to add his

perspective.

DR. DOUGLAS: Disease modifying I think is a really great question because -- and I'll paint some color into, hopefully, what I saw clinically because I've treated probably the most patients in the United States and Europe with this drug. When we think of disease modifying, I think we have to think of many things. One, is the disease melting away and is it changing the trajectory of the course that I would normally see, and do we have any evidence of that?

First of all, what I normally would see in these patients are that they have a rather high severity of proptosis Clinical Activity Score, and within 2 doses, that disease was altered and changed, and getting hugs as they come in for their infusion visit because that course of that disease was no longer severe and progressing but had dramatically improved; and it continued to improve throughout that course of treatment.

So I think that's one line which at least allows you to begin to think about that as being

disease modifying. The second is some of the work that we've shown with the MRIs. Normally, in this disease, what happens is you have an active phase where things get worse and worse, and you have an accumulation of tissue, and then you just stay stagnant. You have large muscles, you have large fat, and things just stay at that state, forever essentially, with very little improvement or very little change, for the most part.

But what we saw in those MRIs, for the first time ever, is a reduction of the muscle size, and we've done volumetric analysis demonstrating a reduction of the muscle size. I can just demonstrate that of not only the muscle but of the fat volume, looking at three-dimensional volume analysis of these; so at least leading us, hopefully, to an idea that this might be disease modifying in those terms also.

DR. HARTNETT: May I just have a follow-up? I guess I'm trying to look for is there a possible biomarker that might help you in the future reduce the number of infusions? I'm just saying like, for

example, if there was a serum biomarker that showed that it was reduced, you might not give as many infusions to patients, where they were having a change in their disease course.

DR. THOMPSON: I understand the point. At this point, I don't think we have a biomarker that we know to be predictive of that. It's certainly a very interesting area of scientific work and something that we'd be interested in looking at. But at this point, I don't have anything to address that.

DR. CHODOSH: Dr. Low Wang?

DR. LOW WANG: Thank you. Of course, in thinking about the safety profile of a drug, we look at AEs, SAEs, and we try to analyze those. But the other part that's important is to try to figure out what patients were excluded. So I went through the different exclusion criteria for study 1 and study 2, and one didn't make sense to me, and that was the exclusion of patients with a bleeding diathesis. I was wondering if you could explain that.

DR. THOMPSON: I'm sorry. Can we bring up -- Dr. Douglas, is this something you would care to comment on?

DR. DOUGLAS: At least clinically, I did not see any patients with a bleeding diathesis that were excluded from the study. I think initially that was for safety purposes only.

DR. LOW WANG: Could I ask a quick follow-up? Why was that included in the exclusion criteria? Was there some signal in previous studies?

DR. THOMPSON: I'm not aware of a signal in previous studies. I apologize, but we'll have to get back to you on that one.

DR. CHODOSH: Could that have been an issue with the fact that they were getting infusions and concern about bleeding related to having repeated infusions?

(No response.)

DR. CHODOSH: Dr. Brittain had a question.

DR. BRITTAIN: I have a follow-up for Dr. Murray's question before the break, and maybe

you have answered this, but I'm not sure.

With respect to the question about identifying the non-responders -- and as you indicated, there weren't a lot of them -- I didn't know if you were answering with respect to baseline, because I guess if you were only answering with respect to baseline, that you couldn't find any identifiers, I would then want to know at what point might the 6-week visit be predictive of what's going to happen longer term, et cetera.

I wonder if you've done anything, any analysis, that might be helpful in identifying whether there's some early time point where it's clear, okay, this is the group of patients that probably won't respond and maybe should not stay on.

DR. THOMPSON: The systematic analysis that I referred to was done on baseline characteristics. What I can say that kind of addresses your question is that we did have patients who were late responders, patients who became responders only at

week 18 or week 24; so hadn't hit their response levels early. I do recognize that's not a perfect answer to your question, but that's the best information we have right now.

DR. BRITTAIN: So was that quite rare?

DR. THOMPSON: We had a few of those responders. Let's see if I can find -- in study 1, we actually had 8 patients who became responders at week 18 for the first time and 2 patients who became responders at week 24 for the first time. In study 2, we had 4 patients who became responders at week 18 for the first time and 1 patient at week 24.

DR. CHODOSH: Dr. Murray?

DR. MURRAY: I wanted to put treatment into context with the incidence and prevalence. You'd commented that you're looking at an incidence of about 25,000 patients per year and a 3-year kind of window of activity with a prevalence of 75,000. Is that your patient pool that you're thinking that you would target as an active indication for treatment?

DR. THOMPSON: A lot of this is going to depend on the details of what the eventual indication statement says. It seems potentially possible that if the indication were to be active thyroid eye disease, those are patients who could be appropriate for treatment.

DR. MURRAY: So to follow up on that, the context of a clinical study with your two trials, looking at a total treatment pool of approximately 100 patients with possible extrapolation to treating 25[000] to 75,000, I know you're going to look at your post-approval follow-up of an additional 200 patients, but where do you think the concern level should be for potential late effects when we look at extrapolating to such a much larger treatment population?

DR. THOMPSON: It's probably optimistic of me to say that I think we're going to treat every one of the 75,000 patients with active thyroid eye disease out there. What I will say is that we think that both through the registry and through active pharmacovigilance, we can continue to

understand the safety profile and inform appropriately.

It is a safety profile that is -- or it is a safety database that is the biggest that exists in this disease, supplemented by information from another indication. And we do propose active pharmacovigilance with enhanced monitoring for adverse events of special interest, as well as a postmarketing registry.

DR. CHODOSH: I'm going to take the prerogative of asking the last question of this session, and I think we hit on it a little bit when we were talking about disease modification. But as far as I can tell, there's no evidence, yet, scientifically, that the presence of this receptor is reduced by treatment.

So then the question is, what is the expectation that it may be necessary to treat patients on and off, for example, for a lifetime with the disease? Because if you prevent the fibrosis and you prevent the long-term consequences, but the receptor is still there, if

you have people that relapse clearly within the one year after treatment -- a substantial number have relapsed -- what's the likelihood of a sufficiently high relapse rate, that patients are on and off treatment over and over and over again, which, again, makes our safety concerns more prominent, obviously?

DR. THOMPSON: I'd like to invite Dr. Douglas to comment on his thoughts about this issue.

DR. DOUGLAS: I think one thing has to be taken into consideration in thinking about this autoimmune disease, which is quite different from other auto immune diseases as far as its relapse, or reactivation as we call it in the field.

Normally, once you get through this stable phase of the disease, they are left in the inactive phase, or stable, where they have these long-term consequences, so there does appear to be this window of opportunity where there's this active disease that's changing. The reactivation rate in the disease once people become stable is 4 to 7

percent lifetime risk, so it's quite a low rate. In fact, myself and Dr. Dailey both treated one patient who had a reactivation and actually responded incredibly well to the second course of therapy.

Now, whether that will be an outlier or not, I don't know as far as my treatment parameter. What I can say is that I treated patients in the clinical program, and they had a multitude of improvements, not just of proptosis, but of all the other values that you saw, but translated into something that was quite robust from the change in their lives.

What I saw, at least as far as our retreatment, was just limited to the reactivation of that one patient. So it's unclear to me as to whether continued treatment will be needed, but what we do know from the unique pathogenesis of this disease is that it's not something that requires ongoing lifetime therapy, even though the receptor stays high, which is your point, but that also it stays high in the natural history of the

course of the disease with a very low reactivation rate. So there is something else going on.

DR. CHODOSH: Thank you very much. I appreciate the presentation by the sponsor. We're going to move now to the FDA presentation, Dr. Chambers.

FDA Presentation - Wiley Chambers

DR. CHAMBERS: Thank you very much. I am going to try and not repeat data that's been presented already, but give you more of a flavor of the types of things the FDA was thinking, and/or directions, and/or discussion that we had with the applicant during the process. That does not mean you need to agree with what we said, did, or interpreted, but just so you have a flavor of where we were coming from.

So ultimately, we're going to ask you to discuss a number of different things. You've already started with some of those as the clarifying questions have come up. They will be things like discussing the onset and duration of effect and whether there is a safety concern for

repeated courses. We think that's both, as far as what's the timing of best treating someone, as well as what happens if you need to give additional treatments later on.

There have been a number of safety issues that have been of varying consequences; not necessarily saying they are necessarily severe, but they're not typical, at least within the ophthalmology community, so we're raising them as further discussion.

The term "active" you've heard come up. We care more about the interpretation, if we include the term, and you've heard that's not been decided, and we're interested in those opinions; whether people will interpret it to be the same -- whether everybody will think of that term as being the same.

We started the discussion about glucose monitoring, the necessity, and timing. We are not necessarily required to come up with specific timing on that unless you think it's important. There are particular adverse events -- muscle

spasms, the hearing loss, diarrhea, infection rate, and alopecia -- that we would like to hear further discussion about as we go further on. And ultimately, we'll end up asking you whether you think the benefits outweigh the risks.

This product, you've already heard, is a sterile, preservative-free, lyophilized product for reconstitution. There will be descriptions about how to reconstitute it. The inactives there raise no special concerns as far as the Food and Drug Administration is concerned, and diluting a product prior to administration is also a common thing with infusions.

The dosing you've also heard. I can say I don't fully understand why you would necessarily think 8 is the best number to come up with. Whether it would be better to do less or whether to do more, I don't have a good basis for. There is no requirement within the Food, Drug, and Cosmetic Act to necessarily get the dose correct or best. The requirement is to come up with a dose administration that provides a clinical result

that's demonstrated in adequate and well-controlled trials.

There's already been a little bit of discussion as far as the key inclusion criteria. The point I want to particularly make is what was studied was people that had the disease for less than 9 months, and whether they were euthyroid, hypothyroid, or hyperthyroid was not critical as far as the entry into the particular trial. And you've already heard the discussion about whether this is active thyroid disease, or if you call it active, what you mean.

There was a clinical activity score, and that was composed of spontaneous orbital pain, gaze-evoked orbital pain, eyelid swelling, eyelid erythema, redness, and inflammation. In order to be entered into the trial, in other words to be called active, you had to have 4 or more of these particular things, each one graded with one point.

The term "active" again is of concern to us because we don't think people will necessarily understand the term, so we want to know whether

it's important to use this term; whether we need to define the term within labeling; or is there a better way to identify patients that enroll in the trial as opposed to using this activity scale.

The clinical data is what you've heard discussed. The safety was derived from using all of the clinical data, so that's both in the intended population as well as from other potential indications. There are some issues with using the oncology data, and I'll talk about that later on. There also is, I believe, one trial that was done in patients with diabetic retinopathy, but that was 5 patients, so I don't think it's much of a database to use.

The efficacy, we are required by the Food, Drug, and Cosmetic Act to base on adequate and well-controlled trials. We certainly think the two trials that you've heard described were adequate and well-controlled trials as far as the definition listed in the Code of Federal Regulations. What you've heard is study 1 and study 2. It was registered with an NCT number. As I just

mentioned, we think both studies met the regulatory definition of adequate and well controlled.

Endpoints can vary in different diseases. We tend to prefer endpoints that talk about how a patient feels, functions, or survives. It's not the only requirement, but it is frequently critical because we are looking to ultimately benefit the patient. We considered proptosis to be important because we believed it led to potential pain, corneal exposure, and diplopia. And to many patients, their appearance is also important, so to that extent, changing proptosis was a critically important endpoint.

The Clinical Activity Score we have criticized in the past. The Clinical Activity Score was some of these particular points. We criticized it because it had equal weighting, and we did not think that all of the particular elements were of equal importance.

For example, pain we think should have been more important than chemosis. Some of the redness and erythema scores are subjective; eyelid

swelling/chemosis are very subjective. Eyelid swelling/chemosis is of questionable significance. The impact on the cornea was not included and diplopia was not included.

This doesn't mean it's not of some useful information; we just didn't think it was good for a primary endpoint. We had discussions with the applicant about endpoints, and this was primarily done at what was the end of phase 2. At that point, the first trial had already been completed and had already included the CAS scale.

We discussed the various endpoints and different options, and while we encouraged during phase 2 multiple different endpoints and did not object to having the CAS score in, we did think it should not have been the primary endpoint for a trial that was ultimately going to support approval. So that was not critical to us because we believe the study could be reanalyzed just taking the CAS score out and redoing the analysis, and we asked the applicant to go and do that.

The results that you've seen have been

analyzed both with and without the CAS score, which we think was appropriate. The original primary endpoint was a yes or no at week 24, and you've already heard this definition; a decrease in overall CAS by 2 points; reduction in proptosis by 2 millimeters; and no deterioration in the other eye.

Because the agency had agreed to the 2-millimeter change in endpoint and the reanalysis, we were willing to accept this reanalysis without any other statistical penalties. Typically, when we change endpoints, we ask applicants to provide analyses in both with and without, and you've seen that gone and done.

This is not an uncommon occurrence. It is not particularly uncommon for us to disagree particularly with the European Union on some of the endpoints in ophthalmology, so we will ask companies to go and redo an analysis. I don't want to leave the impression that there was any particular disagreement between the applicant and the agency. There was agreement on this endpoint,

just not necessarily with the rest of the world, and the agency treated the proptosis endpoint as the primary endpoint for both studies.

You've heard the analysis of using patients as responders. There was also a brief discussion of just using what the mean proptosis score was. Any way you look at this data within proptosis, or at least any way we've looked at the data, there's a clear difference. That difference is present at the first evaluation time point at week 6 and continues to get bigger through week 24.

My recollection is that it's actually even a little bit bigger at week 28 than it is at week 24, both for study 1 and the same thing for study 2; present at week 6 and continues to get bigger through week 24, even if the percentage of people marginally changes for the 2 millimeter. But if you actually just look at the proptosis, it seems like this effect is continuing on, at least through week 24, and I would question a little bit past week 24.

Because it is a systemic treatment, we also

looked at the non-study eye, and the same thing happens in the non-study eye. Not particularly surprising, the baseline is a little bit less for each of those, but the effect is essentially the same.

Diplopia, we considered a primary sign for patients. There is a slight difference in the way these graphs are presented as opposed to what the sponsor presented. They presented and defined within the study an improvement by changing one score on the diplopia score. My personal preference is to go to no diplopia; so these graphs show percentage of people that started with diplopia, and going to know diplopia, it's clearly an improvement in both studies.

Endpoints that were evaluated but we didn't particularly account for the purposes of establishing efficacy, it doesn't mean they're not important, they're just not as critical from our perspective. One was the Graves' Ophthalmopathy Quality of Life score. As has already been mentioned, it had a visual functioning, 8

questions, and appearance, 8 questions.

The agency has put out a guidance document for qualifying a quality-of-life measure. This particular measure has not gone through all of the steps that we ask for in a quality-of-life measure. Again, it doesn't mean it's not necessarily important, but we generally wouldn't accept it as necessarily being a complete quality-of-life measure because it hadn't gone through all the individual parts. Maybe it does; maybe it doesn't. It's just we haven't seen data to support that it fits all those particular parts.

There is some concern, looking at the particular questions, whether there should have been equal weighting between the individual questions. Some seemed more important than others, but this quality-of-life measure uses an equal weighting for each of the different questions, so we did not use it as, basically, data to support the efficacy.

Motility we do think is important. It's difficult to tell which direction is the most

important. When you're using motility, is it better to be able to have improved going up and down or going sideways? All these things were measured in the clinical trial. There is improvement in motility in various directions of varying degrees.

I personally don't know how to judge how much of a change in the number of degrees of motility is necessarily important for the patients. We've tended to use diplopia as a surrogate for that mobility measure. If the diplopia goes away, we've thought that was a better way to evaluate it than necessarily the degrees of motility, but they were actually done in this trial.

There was also clinical measures of severity. It looked at lid aperture, swelling of eyelids, redness, inflammation, subjective diplopia, eye muscle -- you see the list. It raises the question of how much of a change on each of these is necessarily clinically important. Again, you saw us pull out the subjective diplopia, and from my perspective, going to zero is

important, so we did that. We didn't necessarily use the rest of the information, although it was measured.

Of the two studies that were done, one of them does have the extended 72-week data out. It shows approximately 60 percent of the people not relapsing. It's a slight discrepancy between the way we reported it and the way the company reported, and that has to do with whether you got additional corticosteroids. We didn't consider getting the additional corticosteroids to necessarily be a failure, but that number is still somewhere around 60 percent did not relapse.

The converse of that means approximately 40 percent did in that subsequent year, and the question then becomes whether those people should be retreated and what happens if you retreat them; questions that haven't been answered. We also recognize that study 2 is doing the same thing, and we don't have that data. We think that will be useful data, but that doesn't mean we necessarily need to wait for that data before we take an action

on an application.

Labeling, for people that don't understand it, is not a static thing. Just because we initially write a label when a product is first approved doesn't mean it doesn't get changed as we learn more information. So we anticipate that this label, if the product gets approved, will have updated labeling as we learn more about that.

Safety events have both common events and rare events, and you've heard a lot about that already. Ultimately, the safety is a balancing act. We could hold a product back for 30 years and learn a large amount of information about the particular product, but during that period of time, it wouldn't be available to patients. So instead we do this balancing act of how much information is necessary, realizing that we don't have the full safety database when we put a product out on the market. We try and alert people to some of it. We recognize that we don't know all those particular aspects before approval for many products.

I put up here the Rule of Three. Based on

the Rule of Three and probably the fact that we have a decimal system that's based on 10, we've tended to try to identify adverse events that occurred at a 1 percent level, and to do that we ask for 300 patients. This is arbitrary. It's common, but it's arbitrary. The Rule of Three basically says you need 300 patients to be able to identify adverse events that occur if they are real, at a particular rate, at a 1 percent level. Again, I mentioned this not because this is a minimal database, but because this is just what's been commonly done for most products.

As has been already pointed out, this does have an orphan indication. It is a rare disease. It's not an ultra-rare disease. This doesn't just occur in 50 patients in the world, but it also doesn't occur in 300 million people in the world.

The common adverse events, you've already seen, basically, this table that was fairly consistent between study 1 and study 2, both as far as the placebo rate, as well as in the test product rate. You see, as you look down at each of these

tables, fairly consistent rates in both groups. These particular events are all events where they were more common in the teprotumumab group than in the placebo.

You've heard about the gastrointestinal disorders, nausea in particular; infections, a wide range of different infections, no single consistent infection; and alopecia; the muscle spasms are primarily the component of the musculoskeletal connective tissue disorders; and hyperglycemia listed at the bottom.

There were 84 patients treated. There is the continuing information from the OPTIC-X trial, but if I apply the Rule of Three, that means we've identified adverse events that would have occurred at a real rate of about 3.6 percent, but things that are less common than that, we don't think we necessarily would have seen. As has already been mentioned, once you then multiply that by the number of patients that are expected to ultimately take the product, it's a relatively large number of people.

The majority of the rest of the database was in patients with cancer indications. The efficacy in those cancer indications, as has already been mentioned, was poor, which meant the treatment was relatively limited because people came out of the trial as they failed their oncology indication; so they didn't get complete courses of therapy because of disease progression. That limits some of the reported adverse events, as well as some of the adverse events that may be due to other therapies and/or the particular cancer that the patients had.

You've seen this table, basically, before. These are the other studies that were done. The point primarily of this slide is that a wide variety of indications is breast cancer. There are other solid tumors, but they are sarcomas. It's a variety of different indications.

These are some of the adverse events from the cancer chemotherapy trials. I pulled out four of them, the largest, which is the trial that has 310, there's a trial that has 116, and a couple of trials in the 30s. What's identified in yellow

here is to give you an idea of the wide range of reported incidents that occurred with these.

In the large trial, diarrhea was reported in 4 percent, but in a trial a third the size, there was 53 percent. You can go on down -- rash, nausea, fatigue, weight decrease -- and you see the wide discrepancy. This is what makes trying to analyze the oncology indications in the oncology database to try and support this difficult because I don't know which rates to necessarily believe when you have such widely divergent rates.

There's another page that has the same -- we can go on and on about the different events that were reported. Yes, people were treated, but I don't know what an accurate rate is for these particular events.

The safety update, sponsors are required -- you heard the application was originally submitted a number of months ago, and then there's a safety update; so the sponsor provides us with the latest information they have. There were really no new findings that occurred

with the safety update. There was an increase in the frequency of a number of events but nothing particularly new identified as far as more patients have been identified; more patients have been treated.

Again, ultimately, we would like discussion from you on these particular topics. We think efficacy in reducing proptosis has been demonstrated in two adequate and well-controlled trials, but the treatment is not a cure. Some patients will consider additional treatment beyond that observed in the clinical trial, and repeated courses of treatment have not yet been studied.

We will ask you, as we start in the discussion, to discuss the expected onset and duration of effect, and to include in that discussion any potential safety concerns with repeated courses. We think we will have identified adverse events that occurred at a 3.6 percent level or greater, but anything less than that, we don't know that we would necessarily have even seen in the clinical trials to date; so we'll ask you to go

and comment on that, basically, by looking at any of the safety limitations or tell us of labeling that you think is critical to be included if this product is approved.

I've probably said this already multiple times. We're interested in comments about using the term "active." There's already been some discussion as far as monitoring of blood glucose, the extent of whether that's important in everybody, in some people, and is there a minimal frequency that needs to be included within the labeling; so we've raised it as basically the need for monitoring both the initiation and as far as any critical timing.

A number of adverse events have been repeatedly identified with patient administration. A temporal association with the administration has been observed, but a direct causal relationship has not been established for any of these. Frequently, we don't understand the mechanism for a number of these particular events, and that includes things like hearing loss, where there are a limited number

of patients that have the event, but there is an imbalance in these particular events.

You have cases, such as there's a 32-year-old woman who experienced some hearing loss on day 75, so not immediately, and then it resolved the following day. Again, this probably raises more questions than it answers. There are other subjects who the hearing loss went away, but went away with the ending of the administration. We don't know what would happen with repeated courses.

Muscle spasms reported in about a third of the patients, so there is an imbalance; GI, also about a third of the patients, creating an imbalance; infection rate, another thing with up to a third of people being reported and no specific site being identified. So the contribution of teprotumumab -- I'll eventually learn how to pronounce it -- is not known, and alopecia reported again in a higher frequency than in placebo.

So we'll ask you to discuss these particular adverse events, and with that, I'm happy to take any questions.

Clarifying Questions to FDA

DR. CHODOSH: Dr. Yoo?

DR. YOO: Dave Yoo. When you're looking at the safety data, clinical trials looking at the treatment duration, you had listed, for study 1 and 2, both of them had 8 infusions, but as we go further down the list, there's repeated progressions of infusions. Do you have an idea of how many infusions those were for those other studies, for the cancer studies?

The second question is the adverse events for the following slide, you have listed adverse events for NO21157 and the subsequent one. One's for sarcoma and the other's for lung cancer. Those are very different processes, so I don't know that you can necessarily make any generalizable statements because it's treating very different cancers.

So that's more of a statement, but for the first question, do you have any idea how many infusions were done for the cancer treatments?

DR. CHAMBERS: For the cancer treatments.

Most of the cancer therapies were listed as basically treating until progression, and that's the way this study was designed. So yes, I have information on a number of particular infusions. It ranges all over the place. There is no consistent pattern that I was able to detect as far as how many infusions. There are some people that went and did multiple different infusions, and there are others that stopped after one or two.

I agree with you, and that was the point of the slide that had the yellow markers. They are different indications. There are different concomitant therapies. The cancer itself leads to a number of different adverse events. It makes that database difficult to use for a non-cancer indication.

DR. CHODOSH: Dr. Brittain?

DR. BRITTAIN: Can we bring up slide 24? I'd be interested in seeing this same type of figure but extended all the way out to week 72 to see what's happening in the placebo, et cetera. I'm not sure I've seen that, and I don't know if

you have it or the sponsor has it.

DR. CHAMBERS: There is a time point at week 28, but I don't think there's another time point until week 72.

DR. BRITTAIN: But to see the whole graph, all measured time points like this.

DR. CHAMBERS: I didn't do it, but I don't know if the applicant did or not.

DR. BRITTAIN: You haven't reported what happens in the placebo arm. I know you've reported a relapse rate in the drug arm.

DR. CHAMBERS: Well, remember in study 1, people could then get treated, so there's not a true placebo rate continuing on.

DR. BRITTAIN: Then I withdraw my request.

DR. CHODOSH: Dr. Burman?

DR. BURMAN: Thank you. Ken Burman. Did the FDA give any consideration to the preciseness of the diagnosis of thyroid eye disease, especially because some of the patients were euthyroid and may or may not have ever been treated for hyperthyroidism? Also, the utility of the TSI

measurement, which I believe in most orbitopathy patients, due to thyroid disease, is elevated in the vast majority, meaning 90-95 percent of such patients.

Lastly, did the FDA give any interest pursuing other clinical activity scores, such as the published EUGOGO or no-specs criteria?

DR. CHAMBERS: So the initial trial, what's described here as study 1, was an exploration into whether there was initial safety and efficacy. So it was done as a phase 2 trial, and we encouraged the use of a number of different endpoints in that trial, and we accepted the definition used for the inclusion criteria as being valid.

At least within ophthalmology, it is my experience that we use Hertel measurements as for proptosis and have accepted that as being a clinical problem if you see excess proptosis. The second trial then focused primarily on proptosis, and that was the extent that the agency commented that inclusion criteria needed to include.

DR. BURMAN: Real quickly, there are other

causes of proptosis besides autoimmune thyroid orbitopathy.

DR. CHAMBERS: We would absolutely agree. However, if this fixes the proptosis regardless of the cause, we think it would be of clinical benefit.

DR. CHODOSH: In my experience, most patients that are diagnosed with thyroid eye disease have had a scan of some sort. I didn't hear from the sponsor what proportion of patients were diagnosed with the addition of a scan, because there are specific findings on scan with regard to muscle body involvement that help ophthalmologists to define that it's thyroid eye disease as opposed to a tumor, for example, which could cause proptosis.

Dr. Murray?

DR. MURRAY: Dr. Chambers, I've shared the concern of active as really a lax definition for most clinical practitioners. With a drug that's been evaluated in 90 patients, extrapolating to a large potential population source of treatment, it

seems to me that it would be reasonable to have a high threshold for the definition of active disease, at least with the initial release of the drug. I wonder if you have any comment about how that's been done in the past maybe with other trials like this, with drugs and rare diseases.

DR. CHAMBERS: So as you might guess, it's probably all over the map. The clinical trials are meant to inform people of the potential safety and efficacy of a particular product, but we recognize it is not the same population as will necessarily be used in the future. We have the ability to extend that population for approval to wider than what was studied if we think it's relevant to go and do so. We have the ability to restrict it if we think, generally, there are safety concerns that would suggest we should restrict it, or efficacy concerns that we think it only works in a particular population.

That's part of the reason for bringing the product to the advisory committees, to hear your thoughts on whether we should expand the population

wider than what was initially listed or to limit the population to less than what was initially studied.

DR. MURRAY: So my issue with this is I'm not really sure what the inclusion criteria by labeling this active really actually identifies. I think there could be a broad interpretation, clinically, within the population of clinicians treating these patients as to what is active disease and not.

Proptosis is clear and really very simple for us to identify, and appropriate imaging for the patient with proptosis, I think, is really fairly routine, but labeling something proptotic and active from thyroid disease I think is a different extension. So I just wonder if we could have some comment from the audience and the clinicians as to how they would feel about that labeling.

I got a suggestion that you would be interested in almost the majority of your thyroid patients being eligible to be treated. It does seem, from my perspective, the efficacy is

outstanding in an area that we have not, really, had alternative treatments for that are FDA approved. But when the number's that small and there's a population risk of serious adverse event that we're missing because we've only evaluated such a small population, it makes me think that maybe restricting access to clearly active disease, however we define that, might be a safety approach for the labeling of the drug initially.

DR. CHAMBERS: When we get to the discussion portion of the committee meeting, we encourage to hear from a large number of people on whether we think active should be included in the term, either alternatives, or definitions.

DR. CHODOSH: Dr Low Wang?

DR. LOW WANG: Thank you. In terms of thinking about an eventual discussion question about the need for glucose monitoring, I don't feel like I have enough information right now. We were given a little bit of information about the highest glucose value that was seen and when that was seen, as well as the highest A1c, but how soon did

hyperglycemia occur? What was the degree of elevation, et cetera, in the population?

DR. CHAMBERS: I'll let the applicant go and answer that. We do have that within the database, but I won't be able to come up with it today.

DR. THOMPSON: Hyperglycemia onset was seen as early as following the first dose and as late as during the follow-up period. So it really was seen throughout treatment course and later.

DR. CHODOSH: Dr. Atillasoy?

DR. ATILLASOY: Just two quick questions; first on efficacy and slide 24, you mentioned that at week 28, you actually see an enhanced separation of the curves. I don't know if we have that to display. Along those lines, the measurement was taken prior to that last infusion, I take it. In terms of the visits from the patients, just a question about when you're measuring and when you're administering.

So should I infer, for example, that the patient received a dose at week 24 and came back either 3 weeks or 4 weeks later? Maybe I could

just get clarity on that.

DR. CHAMBERS: The applicant can correct me if I'm wrong, but there are a total of 8 infusions. The first one is done at time zero, and then you have week 3 as one, so week 6 is two. And if you go on, week 21 is the last infusion, so week 24 is 3 weeks after the last infusion.

DR. ATILLASOY: Okay.

DR. CHAMBERS: And then there was also an additional visit for most patients at week 28, but not everybody.

DR. ATILLASOY: You made the statement that we're seeing enhanced separation, so an additive effect. Did I get that right?

DR. CHAMBERS: Correct. If you look at millimeters of basically off the Hertel, it continues to widen throughout this course of therapy and continue afterward. But we don't continue to follow them at either 6-week intervals or any kind of interval afterward. So I don't know at what point it goes and reverses or stabilizes. I only know 7 weeks after the treatment.

DR. ATILLASOY: Thank you. One other question, just on the safety side, just being a dermatologist, the alopecia, were any particular trends, types of alopecia seen? Was it just generalized and what we call androgenetic or any cases of alopecia areata, which might be more autoimmune. Do we have any specifics from the agency or the sponsor?

DR. CHAMBERS: I'm only aware of it being reported as alopecia.

DR. THOMPSON: Alopecia was seen more frequently in patients on teprotumumab than placebo. In the double-masked period, that was 13 percent versus 8 percent. When we had any further specification, the alopecia was noted as involving the head, the body, the axilla, the pubic area.

DR. ATILLASOY: I see.

DR. THOMPSON: Onset for most began 3 months or longer after initiation. All of them have been non-serious. None of them were reported as alopecia areata, and we do have some that are

resolved at this point.

DR. ATILLASOY: Very good. And personally, I don't have a significant concern about that, given the opportunity of this product.

DR. CHODOSH: Dr. Atillasoy, can you comment on what that means, that it was diffuse as opposed to the scalp?

DR. ATILLASOY: I just view that as non-specific. There's different types of alopecia, as you know, totalis, universalis, but I'm not hearing any autoimmune phenomenon. You would think that either with the circular alopecia areata or complete loss, you might posit it autoimmune, but based on what I'm hearing, I don't see evidence for that.

DR. CHODOSH: Thank you. Dr. Stamler, you had a question?

DR. STAMLER: Yes. Thank you. I have a question, again, about the diagnosis for the study. In the inclusion criteria, the diagnosis is stated as having thyroid eye disease, having Graves' disease, but patients who are in severe disease and

come to a oculoplastics clinic, it's really not much of a question about what they have.

I run a corneal practice where I see a lot of patients with dry-eye symptoms, and I see a fair number of patients with what I consider mild Graves' disease, who are euthyroid. They don't have diplopia, they don't have severe proptosis, but I think like everything, there's a bell-shaped curve. I think that's the fat part of the bell-shaped curve.

So I'm concerned that there are a lot of patients who can have the diagnosis of thyroid eye disease but are not severe and not included in this type of study, which brings up a couple of questions in my mind. One is should we discuss some sort of threshold for treatment of disease with relation to the adverse events? We have to balance the adverse events versus the severity of disease, and should we find some line that we draw for that? We haven't talked about that yet.

With regard to the diagnosis, proptosis, we just talked about Hertel measurements in proptosis,

using those synonymously. It's not really the same thing. When I'm evaluating people for dry-eye disease, I always do a Hertel measurement, and I always have Graves' disease in the back of my mind. I've done Hertel measurements on hundreds, perhaps thousands, of patients who don't have rave's disease who are normal, and there's quite a variability in those patients of normal.

We have an average Hertel measurement here of around 23, but I see a lot of patients in my clinic that have measurements of 23 but do not have Graves' disease. So I don't think there's a Hertel measurement that you can use as a cutoff and say these people have thyroid eye disease or not. I think a change in value is much more useful. But without baseline, premorbid measurements, we don't know that in this disease.

I guess that's more of a comment than a question, but I think perhaps we should discuss how much of the severity of the disease deserves treatment. If we okay a hammer among the physicians, we're going to find a lot more nails,

and some of those nails might be kind of small.

DR. CHODOSH: I think that relates back to the question of active, and what does that mean, and how should it be defined.

DR. STAMLER: Yes, I think that's related to active, but it's a little bit different, too. It can be active, but mild, and does that deserve this treatment or not? Some people without proptosis, without diplopia, they're very bothered by their symptoms, and perhaps they do deserve treatment, but it's I think worth discussion.

DR. CHODOSH: Dr. Chambers, did you feel a need to respond to that?

DR. CHAMBERS: I agree, and that's the point of having this discussion.

DR. CHODOSH: Ms. Schwartzott?

MS. SCHWARTZOTT: I have a question about the diabetic patients. Were both type 1 and type 2 tested, and are there additional safety risks that might prevent a type 1 diabetic from taking this medication?

DR. CHAMBERS: There were relatively few

diabetic patients that were included. My recollection is both type 1 and type 2. But again, we're talking 5 to 10 patients. I'll let the applicant go into the exact numbers.

DR. THOMPSON: We did have in the teprotumumab arm 10 patients who had preexisting diabetes, either type 1 or type 2. These patients were more likely to experience events of hyperglycemia, but they were managed with either modifications to their existing medications or additions to their existing medications.

DR. CHODOSH: Dr. Low Wang, go ahead.

DR. LOW WANG: Can I just follow that up? It looks like from the briefing document that in the OPTIC-X study, the patients who experienced hyperglycemia did not have a preexisting history of diabetes or impaired glucose tolerance. I think there are a few patients where this hyperglycemia is still ongoing even though they're not receiving treatment.

Could you comment on that?

DR. THOMPSON: There are new onset

hyperglycemia that had been seen in patients in OPTIC-X. We have 8 patients who were not diabetic who have new onset adverse events of hyperglycemia. So far, five of those events have resolved. The event durations have ranged a great deal, frankly, from about a month up to almost a year. Events are ongoing for three remaining patients, and 2 of the 3 of those patients are on Metformin.

DR. CHODOSH: Thank you so much, Dr. Chambers.

We're going to break for lunch. We're going to restart this meeting at 12:25, or we can do 12:30. I'll give you the last five minutes.

(Laughter.)

DR. CHODOSH: Please take personal belongings you may want with you. Committee members, again, please remember there's no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you. See you at 12:30.

(Whereupon, at 11:25 a.m., a lunch recess was taken.)

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

(12:30 p.m.)

Open Public Hearing

DR. CHODOSH: Welcome back. 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 open public hearing session of the advisory committee meeting, FDA believes it's important to understand the context of an individual's presentation.

For this reason, 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 you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee

if you do not have 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 again; again, 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 consideration of the issues before us.

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

With this, I'd like to move to the first. Will speaker number 1 come to the podium and introduce yourself? Please state your name and any

organization you're representing, for the record. Thank you.

DR. PATTERSON: My name is Dr. Nancy Patterson. I'm from North Carolina, and the National Organization of Rare Disorders paid for my travel. I founded the Graves' Disease Foundation in 1990. Its purpose was to educate, encourage, and empower patients and caregivers dealing with Graves' disease.

When the foundation started, there were no support groups. There was no place to get information either about the condition, how it was treated, or how to live with it. Today, we provide support groups, multistate conferences, online support, one-to-one telephone support and research, but I'm here to share my experience with you about the most debilitating consequence of Graves' disease, thyroid eye disease.

In 1987, I was diagnosed with both Graves' and TED. At that time, there were no treatments for TED. During the active phase, which for me lasted three years, it could be managed. They

could use steroids, eye drops, ointments, tape your eyes at night, prisms in your glasses, ice packs, punctal plugs, tarsorrhaphies, ice packs, but nothing could be done to prevent it; they could only manage it. I had all of those management techniques except radiation, and I still tape my eyes closed every night, as I have done for 33 years.

This lack of any treatment has not changed. For a disease whose most formidable complication is pressure on the eye from the excessive swelling that can cause permanent blindness, due to the development of teprotumumab, now this can change. You've been made aware of the symptoms. They subside at the end of the active phase. However, if the swelling and inflammation have become scar tissue, the only treatments remaining are surgical.

In the past 30 years, I have had multiple eye surgeries. I still have most of my inactive symptoms, including double vision, poor depth perception, dry eyes, and extreme light sensitivity. When there are two identical cars on

the road going in two different directions, you don't know which one to follow. When the car is coming at you and their lights cover the entire highway, you don't really know where they are. That therefore means, now, that I am legally blind and unable to drive. On the lighter side, your Christmas tree doesn't need as many lights because there's two of all of them. On the darker side, because of Ted, I'm unemployed.

I had a very successful private mental health practice for more than 30 years. Because I no longer drive, something we all take for granted, I can no longer get to work or anywhere else I need to go. Eventually, your friends tire of always having to do things at your house and contact diminishes. I can't hop in my car and drive to Florida to see my family. I can't see the music in my church and sing in the church choir, and I can't even read large-print books.

This experience is not unique to me. I stopped counting it over 17,000 phone calls the first half of the Graves' Foundation's existence.

I recently spoke about quality of health to a conference in Pisa. In a survey, one young woman reported, "My biggest problem is I still have not a clue about what's going on. From time to time, I don't feel anything and all is fine, and it seems to have stopped, and then all of a sudden, it comes back."

She exemplifies the lack of known treatments for TED. This woman has only had TED for less than a year. She is young, and her life is just beginning. For her, having teprotumumab could mean avoiding much of what it and others -- I can't read it -- you will hear from today have experienced, the fear of the unknown; the surgeries; the loss of independence; the financial impact of lost careers, income; isolation; and damaged relationships.

What I want this committee to remember is that all of this now may be prevented. Years of research and testing have proven that if treated early, TED can be significantly altered or prevented. It will not help those of us with long-term TED, but for those who will be diagnosed,

there is hope.

The key is getting treatment early and getting patient-centered treatment. One size does not fit all for rare disorders. If the timeline is unnecessarily delayed, efficacy is diminished. This must not happen. Please keep this in mind as you review this new treatment that could bring help and hope to all of those who will be diagnosed with TED in the future. Thank you for your time.

DR. CHODOSH: Thank you very much for that comment.

Can we have speaker number 2, please?

MS. ARNSTEN: Thank you. I'm supposed to get 6 minutes, though; it's on 5.

MS. ARNSTEN: Thank you. Kathleen Arnsten. I'm a patient advocate and president and CEO of Lupus and Allied Diseases Association. I have nothing to disclose personally, but as a charitable organization, LADA receives program service funding for many stakeholders, representing various viewpoints regarding healthcare issues. However, we solely embody the patient perspective here.

Good afternoon and thank you for the opportunity to provide our patient viewpoint regarding the BLA for teprotumumab for the treatment of thyroid eye disease, or TED, and you should have our written comments in your folders. I'm here today as an individual who knows firsthand that we urgently need new treatments for people struggling to live with debilitating autoimmune conditions and urge you to vote to approve this BLA to address the significant unmet medical need of TED.

I've been diagnosed with multiple autoimmune conditions, including but not limited to lupus, Sjogren's syndrome, myasthenia gravis, nephritis, and Graves' disease. I currently take 47 drugs a day and have allergies to both active and inactive ingredients in drugs, and I am blind in my right eye.

I lost my vision due to herpes zoster and reactions to eye drops. My medical care requires careful monitoring by my healthcare team, and I am an integral part of that team. One of our primary

goals is to protect and preserve the sight in my left eye. There are no cookie-cutter products in existence for atypical complex patients like me. My physicians and I eagerly wait for more efficacious and safer innovative treatments that do not ablate the entire immune system and cause detrimental effects.

Those promising and groundbreaking treatments are referred to as targeted treatments and are usually biological medicines. Biological products are extremely complex drugs and molecules patterned after human tissue installs that have the ability to target the underlying cause of some diseases.

Teprotumumab is a biologic drug and a promising cutting-edge treatment that reduces the underlying autoimmune pathogenesis of TED. TED is a serious progressive vision-threatening and life-altering autoimmune disease. It begins with active TED and can last up to three years, and obviously diminishes a person's independence, ability to work, and self-confidence.

As it progresses, long-term irreversible damage can occur causing vision loss. It is usually seen in patients with Graves' disease, but it is a separate disease requiring separate treatment. Effective management requires early diagnosis and accurate treatment during a narrow window of time, and monitoring to identify the best opportunity for intervention.

TED only responds to medication during active illness and inflammation. Once it becomes inactive, treatment options are limited to complex surgery with potential complications. Since there are currently no FDA-approved treatment options for active TED, patients are often prescribed glucocorticoids and the immunosuppressant drugs which come with undesirable and toxic side effects.

Because of my conditions, I followed a 31-year regimen of steroids, suffering permanent damage, disfigurements, and even weighing 221 pounds at one point. Any of us who have taken steroids can tell you they are the drugs we love to hate. They can save your life and fight

inflammation quickly, but this comes with horrific impacts such as glaucoma, cataracts, hypertension, diabetes, obesity, atherosclerosis, bone thinning, infection, susceptibility, elevated cholesterol, manic feelings, stroke, and the appetite equal to that of four growing teenage boys.

I have also taken immunosuppressant drugs for decades and could assure you that they destroy the immune system and can cause infertility and miscarriages. We get numerous infections multiple times a year, and some of us even end up with cancer. And here's my favorite. We're given prescription drugs to address the side effects of our other medications, which is just ludicrous.

Many current therapies are just band-aids, treating the symptoms and never getting to the root of the problem. We desperately need safer, more innovative treatments that address the disease pathogenesis while impacting what matters most to us patients, reducing symptoms and improving functioning and daily quality of life.

As a targeted treatment, teprotumumab holds

tremendous promise and therapeutic benefits for people like me. Access to appropriate medication dramatically improves disease outcome and quality of life; reduces the severity and frequency of disease activity; and slows down progression, enabling people to remain functional and productive. Individuals struggling to live with TED experience long-term functional, emotional, and financial burdens. TED has a significant effect on patient wellbeing.

I was diagnosed with Graves' disease and ophthalmopathy years ago and received radioactive iodine therapy. I then developed radioactive thyroiditis and became hypothyroid. I've been on a thyroid hormones since then. Because I was not euthyroid at the time of the radiotherapy, I am at a higher risk to develop TED.

The odds also increased with each decade of age progression. It is extremely important for my vision to be preserved in my left eye for me to remain functional. Given my risk to develop TED, I am extremely thrilled and hopeful with the positive

results of the pool efficacy data of the phase 2 and phase 3 clinical trials.

As a leader of LADA, a national patient advocacy organization led by people who struggle daily to live with serious life-altering and life-diminishing diseases of unmet need, I must switch my hats to also state that we are ecstatic over the encouraging combined results of the teprotumumab clinical trials. The study results demonstrated positive impacts on visual function and improvements in patient quality of life.

I would like to thank you again for the opportunity to share our perspective as you evaluate teprotumumab for treating active TED and strongly encourage you to support this application, given the positive results of the clinical trials and profound impact the treatment will have on improving the lives of those affected by TED. We applaud you for recognizing the importance of the patient voice, especially since we are the sole stakeholders who experience the benefits and risks of new drugs. Thank you again.

DR. CHODOSH: Thank you so much.

Will speaker number 3 step to the podium, introduce yourself, and state your name and organization for the record? Thank you.

DR. RAJAII: My name is Fatemeh Rajaii, and I'm an oculoplastic surgeon at the Wilmer Eye Institute. First, I'd like to disclose that I have served as a consultant to Horizon Therapeutics in an educational capacity, and I've been happy to do so because of the promise I think teprotumumab holds.

I know you've spent a significant amount of time this morning learning about the data and science behind the drug, so of course I'm not going to use this time to speak about that. Instead, I'd like to use this small amount of time to let you know about my experience in treating patients with thyroid eye disease in order to help you understand why so many of my colleagues in the field of oculoplastic surgery and endocrinology are so excited about the possibility of having this drug available to treat our patients.

Like most oculoplastic surgeons, my firsthand experience with the drug is limited. However, as one of Dr. Douglas' fellows at University of Michigan, I did have the opportunity to occasionally examine patients in the phase 2 trial. Though we were blinded at the time to patients assigned to treatments, I remember many of us, even at that very early stage, had the sense that some patients were doing much better than we would expect, given the natural history of thyroid eye disease, and there was a lot of excitement that came with that.

Since that experience, I've followed the trials and results with great interest, only to see that early excitement continue and grow. Each time I read about data or see data from the clinical trials presented, I'm struck by the magnitude of the results documented, specifically in terms of proptosis improvement and improvement in diplopia; although, as you know, there are many other variables that have been improved such as quality of life and others. But again, I don't want to

discuss the science; you don't need to hear that from me.

I would like to convey to you, though, that it's not just endocrinologists and oculoplastic surgeons who are excited about the drug; our patients are as well. About two years ago, I actually had a patient bring in a New England Journal of Medicine paper, that reported the phase 2 results, to her visit to see me. She'd been searching on the internet for treatments for her disease and wanted to try it. She'd asked her endocrinologist about it, and of course he couldn't prescribe it, so she came to ask me if I could prescribe it.

For more background, the patient had moderate to severe active thyroid eye disease and had already been treated with steroids and orbital radiation with no sufficient response. This intelligent patient with no medical background was researching on the internet to find if there was anything else she could try and happened upon that paper.

When I explained to her that I agreed the early results were exciting, but at that point it was only available to patients in the clinical trial, she asked me to get her into the clinical trial. Unfortunately, we weren't able to do so due to the length of activity she had, so we continued to take care of her. Unfortunately, she went on to develop optic neuropathy, necessitating bilateral orbital decompressions, and she's still in the process of her surgical rehabilitation for the disease two years later.

I still take care of her, saw her recently, and we still actually talk about the drug. She wants to know how it's doing, how things are doing, and I think we actually both wonder what would have happened to her and how her outcome may have been different if she had been a candidate for enrollment in the trial.

This was of course an uncommon interaction, but I think it highlights the need for effective therapies to treat patients with thyroid eye disease and our hope for therapies that could alter

the disease course. What would an altered disease course mean? Although I'm a surgeon and I love doing surgery, I hope that an altered disease course will mean fewer surgeries and better outcomes for patients with thyroid eye disease.

I would prefer to not have to tell patients that we will observe them for a period of two to three years, waiting until they either develop severe vision-threatening disease or until their disease activity burns out to be able to spend another one to two years surgically managing the results, the resulting disfigurement and disability from the disease process. I hope to see fewer and fewer patients who have moderate to severe inactive disease with severe disfigurement and ocular surface disease from proptosis and eyelid retraction; disfigurement from proptosis and strabismus; and disability due to strabismus.

Although I don't think any surgeon likes to talk about it, we all have either treated or seen patients with severe disfiguring and disabling disease who we simply cannot treat well enough with

surgery. This brings to mind a patient who I met as a second opinion consultation. The patient had had multiple orbital decompressions, strabismus surgery, and eye lid surgery, all with the goal of rehabilitating her thyroid eye disease and all reasonably done. However, she still remained proptotic with poor eyelid closure, causing her severe individually significant dry eye.

Honestly, there are just limitations to surgery, and although I remember a lot about my interaction with her, what I will never forget is that her main complaint was not even the pain or the visual dysfunction from the dry eye; that was an important secondary concern. Her main complaint and the reason she broke into tears in the chair was that since having thyroid eye disease, she'd had the horrible experience of being in the grocery store and noticing that children were scared of seeing her. Imagine the impact of being so disfigured that you elicit that reaction from children.

Again, unfortunately, given the severity of

her disease, the options are very limited. But I can say with a high degree of certainty that all of us who take care of these patients are excited about having medical therapy that may alter that disease course. Thank you again for the time to speak.

DR. CHODOSH: Thank you.

Will speaker number 4 step to the podium and introduce yourself, your name, and any organization you're representing for the record? Thank you.

DR. SMITH: I am Dr. Terry Smith, the Frederick Huetwell Professor of Ophthalmology and Visual Sciences, and professor of internal medicine at the University of Michigan Medical School. I have been issued several U.S. patents for the use of IGF-1 receptor inhibitors, of which teprotumumab represents one, in autoimmune diseases, which are held by UCLA. I am a paid consultant for Horizon Therapeutics.

This afternoon, I am lending my strongest support for the approval of teprotumumab for the treatment of thyroid eye disease, not only because

the molecular and cellular rationale for this therapy was born in my laboratory two decades ago, but because my professional life has been dedicated to caring for patients with Graves' disease and TED. I am reminded regularly of their profoundly unmet need that the disease imposes on their daily lives every time I treat these patients and am faced with their diminished quality of life.

My professional journey with Graves' disease began as a medical student when I first encountered this disorder. The patient not only exhibited very serious thyrotoxicosis, but also experienced severe ocular discomfort and facial disfigurement. This encounter, and subsequently managing similar patients, played a large part in my choice of clinical subspecialties.

As you have heard earlier, we have very little medical treatment to offer our patients since no currently available medical therapies for TED have been approved by the U.S. FDA. We remain largely dependent on the use of high-dose glucocorticoid steroids to alleviate some of the

discomfort caused by the inflammatory and congestive components of the disease.

Importantly, these agents fail to alter disease severity, its natural course, or the necessity for surgical intervention once the disease has stabilized. Their use comes with substantial side effects. Further, the results of the rehabilitative surgeries currently employed for TED are frequently suboptimal. They have unpredictable outcomes, can reactivate the disease, and often require multistage surgical procedures.

The entire rationale for the development of teprotumumab resulted from several experimental observations made in my laboratory. Thus, elucidation of the mechanistic underpinnings for the disease has resulted in the identification of a plausible molecular target, namely the insulin-like growth factor 1 receptor. This has been borne out by the two successful clinical trials, the efficacy and safety results of which have been presented to you this morning.

The potential for teprotumumab to

dramatically impact the quality of life and function of our patients with TED in my view underscores the importance of this therapy gaining FDA registration. I therefore urge the committee to look favorably upon the application for approval of this drug in the strongest terms possible. Thank you.

DR. CHODOSH: Thank you very much.

Will speaker number 5 step to the podium, introduce yourself, your name, and any organization you're representing for the record? Thanks.

MR. BARELA: Good afternoon. My name is Ronald Barela. My travel was supported by the National Organization of Rare Disorders. My wife Vicky and I now live in a very rural area of Washington State. My purpose and hope in sharing my story with you is to enlighten you about the impact of thyroid eye disease on the lives of not just the patients, but also the effects on their loved ones, co-workers, and the community as well.

Prior to retirement, I had dual careers. I was in law enforcement for 33 years and

simultaneously was a commissioned officer in the United States Coast Guard Reserve, serving ashore and at sea from the Bering Sea to Cartagena, Colombia, and points between.

Going back a few years, in 1992, I had noticed that my eyes were tearing significantly with no apparent reason. I also had periods of eye pain, but was busy with my careers and a forthcoming marriage in September. One day in December, while preparing for work, my eyes once again began tearing profusely, my vision blurred, and I became very dizzy. Looking in the mirror, I saw that my eyes had severely crossed and bulged out. I looked like the old movie actor Marty Feldman.

I called my new wife, a veteran registered nurse, who with a look of shock immediately realized that something very serious was happening to my eyes. The next day, I went to the hospital and began a two-year period of various medications, x-ray treatments, and all of the eye surgeries known to each eye, each one requiring a lengthy

recovery period before the next.

During this two-year period, I varied from total blindness during surgery to vision that qualified as limited, legally blind. Of equal distress was that my vision difficulties caused me to have a constant loss of equilibrium and dizziness. These problems prevented me from performing my duties either as an armed, badge-carrying police sergeant or a military officer.

When I was able to leave the bedroom, I would have to lean against the wall as I walked to avoid falling due to loss of equilibrium. On several occasions, while waiting for public transportation, I fell to the ground due to dizziness, which caused onlookers to assume I was intoxicated. Of course, driving or operating any form of equipment was out of the question. On one occasion, a bus driver refused to let me on his bus, thinking I was intoxicated.

My police department allowed me to use vacation and earned leave during times when I was

having surgeries, and other times I was allowed to perform indoor seated basic functions in the police department. However, I knew that these arrangements could not last forever, and was told as I approached the two-year mark that I would have to be able to requalify for most of my occupational tasks or to retire. I was told the same by the Coast Guard.

Of note is that during this time my wife had to lead me and take me everywhere I needed to go. During times of total blindness, she fed me and taught me to feed myself. For one who was in positions of control and assessment of everything about me, this was exceedingly difficult and wore heavily on my wife, who had to observe and compensate for my deficits. With severe double vision, I was not able to visually coordinate pulling anything or moving anything from one location to another. That provided considerable mirth for my associates and visitors, much to my chagrin.

Ultimately, after a long two-year period, I

thankfully was able to resume most of my duties and reach retirement tenure with the police department and the Coast Guard. However, in addition to the lifetime effects of my thyroid eye disease, the long lasting effects of multiple surgeries themselves have a lifetime detrimental effect on my eyes. I have had subsequent eye muscle and lid surgeries and will always have a degree of double vision.

I hope my story has helped you understand the impact of TED not only on patients, but everyone around them as well. Had the treatment you're reviewing today been available, I believe not only could my eye disease have been treated faster and without the effects of multiple surgeries, but my recovery would have been more if not all complete. I believe this medicine, if approved, would provide great relief to a lot of people. Thank you for allowing me to share my thoughts on this matter.

DR. CHODOSH: Thank you.

Will speaker number 6 please come to the

podium? State your name and any organization you're representing for the record. Thank you.

MS. SCHATZ: My name is Susan Schatz. The National Organization of Rare Disorders supported my travel. Thyroid eye disease is a rare disease that resulted in my loss of income, disfigurement, huge emotional losses, high anxiety, and reduction in my joy and happiness. I traveled here today from Monterey, California to share my story with you because I would do anything I could to help even just one person receive medical treatment for this disease, that would help them avoid the journey I've experienced.

I'm a self-employed, private practice speech pathologist, and I see mostly neurologically involved young children who have speech, language, hearing, cognitive, and behavioral disorders. My income depends on working directly with the patients in my office. One day, I experienced my first symptom of thyroid eye disease, which was a droopy eyelid in 2005. While I searched for the right doctor, the right diagnosis, and the right

treatment that year, my patients began asking me, "Are you able to see my child?" "Can you safely work with them?" And I didn't know what to answer.

While I was working with a child who was having a tantrum, he was on the floor and was kicking his legs in the air, but suddenly I noticed this child had four legs. Now, I knew cognitively that could not be correct, but that was what I saw. And as I was driving home from work, there were three yellow lines on the left side of the road and two white lights on the right. I thought maybe I was just tired, but when I tried to look at a cooking show on TV, there was one chef with four arms and four pans, but he only described one cooking procedure in one pan. I knew this was not good.

Strangers everywhere I went asked me what was wrong. I was having difficulty sleeping, and I was filled with fear. I didn't laugh, I didn't want to do anything with friends, and I certainly didn't want to make any plans for vacations. My significant other began to distance himself, and

eventually he no longer wanted to be committed to our relationship. He said that I was no fun to be with, and he was right, so I was scared and alone.

I had only 10 percent mobility of my right eye and marked diplopia. Here I was with a disfiguring face, unable to read; couldn't sleep; couldn't drive; couldn't even measure water for cooking; couldn't pay bills; handle the TV remote; drive or hike -- I walked into a tree -- basically, any of the things that brought me joy. And as I have no family, I really had no one to help me.

When I was receiving orbital radiation therapy in 2005, I was unable to work. Each visit to Stanford Medical Center entailed about a two-hour drive going and coming, in addition to the procedure. I had to rely on friends to take me since I was unable to drive.

From 2005 to 2010, I had five eye surgeries. Many of these surgeries, I had to pay out of pocket because the insurance did not cover them or the doctor did not accept the insurance. This has had a huge negative financial impact on my practice, my

life, and my retirement, which has been postponed.

I am currently able to see without diplopia when I look straight ahead. However, when I look up, or to the left or right, the diplopia is still present. I am anxious when I travel alone, so I attend fewer social events and I go to fewer conferences. But I traveled here today to share my story with you because I want you to understand what this disease does to a person's life; all the small things that add up to social isolation, ongoing fear, and financial loss.

I would have been so grateful to have received teprotumumab as a treatment option rather than orbital radiation, steroid therapy, and the multiple eye surgeries I have gone through. I hope that in your decision today, you give others that option. Thank you.

DR. CHODOSH: Thank you so much.

Will speak your number 7 come to the podium and introduce yourself, your name, and any organization you're representing, for the record? Thank you.

MS. LABADIE: Good afternoon. My name is Wendy Labadie. I'm from Omaha, Nebraska, and my travel was supported by NORD. I volunteered to travel here today because I benefited from teprotumumab, and after hearing everybody else, I'm very grateful that I did. I had a 2-millimeter reduction in one eye and a 3-millimeter reduction in the other. Just what does a 2-millimeter or 3-millimeter reduction mean? For me, it was life-changing.

In December of 2017, I was told I looked bug-eyed when taking Christmas photos, and I was frequently told I looked tired. Well, as a mother of boys and working full time, I just was tired. So I just deleted every picture that I took and just tried to shake off the comments. But by January of 2018, I had problems just completing my everyday activities. At work, I had to sit in a dark room and often wore sunglasses while looking at the computer screen. The majority of my day was spent with one eye closed, and none of it helped.

I was diagnosed with Graves' disease and

thyroid eye disease in January of 2018. While there were options to treat the Graves' disease, I was slowly learning there was not much I could do to prevent the deteriorating condition of my eyes. Driving became difficult. I drove with one eye closed due to the severe double vision, and I struggled with night driving because of the oncoming lights. I also had blind spots in my peripheral vision, so changing lanes became very difficult.

I quit driving long distances anywhere I was not familiar going. Even tasks as simple as running errands became difficult because fluorescent lighting bothered me. I had to leave Costco one day in tears after I ran my cart into someone because I didn't see her out of my peripheral vision. After that, I came up with excuses not to do the shopping or at least to have my husband go with me.

The double vision also made things like my regular fitness routine difficult. Just imagine trying to jump on a box when you see two of them

and just hoping you hit the right one. I also had some vision loss when looking down, so running on uneven surfaces or even just walking when it was icy out became a challenge. Around this time, my stepson became engaged. I was absolutely thrilled for them, but my excitement was severely hindered by my concern about how I looked. I was so self-conscious, and I did not want to meet new people, including his future wife's family.

In March of 2018, I saw a TED specialist for the first time. I left that appointment discouraged. I was told I could undergo a series of steroid injections, but the list of side effects seem to outweigh the little benefit. My only other choice was to wait it out for a year or two until I was not in the active phase, and I'm just not very good about waiting it out.

So shortly thereafter, I stumbled upon someone in a TED support group, and she was so excited about meeting an expert in Beverly Hills. I opened the thread and could not stop reading all the wonderful comments about Dr. Douglas. I

googled Dr. Douglas, which led me to the information on the trial. I skyped with Dr. Douglas and felt hope for the very first time.

By spring of 2018, while waiting to start the trial, I hit my bottom. Watching my sons play baseball and shoot trap, it came close to impossible. During trap competitions, I could not see if my son hit the orange clay, and at baseball, I had to frequently ask people what happened when the plays were out in the outfield.

Nighttime games were also very difficult to sit through because of the lights. I had to watch those with my sunglasses on. I was afraid, though, that if I didn't sit there and tough it out, I'd never be able to watch them play again. I tried everything. I had multiple pairs of prism glasses. I had special coding on my glasses for computer glare. I had glasses made for nighttime glare. I had sunglasses that went over the prism glasses, and I even had one very stylish eye patch.

In June of 2018, I had my first infusion of teprotumumab. I don't recall the exact turnaround

point, but by the time my stepson was married in December of 2018, I felt good about my appearance, and I enjoyed meeting all of my new daughter's family. Today, I have resumed almost all of my previous activities. I stand here today, happy to report I only see one of each of you. I am able to watch my kids' activities, I'm able to drive at night, and I can work.

In September, I played golf for the first time in two years. We won't talk about my score. These are some of the things I feared I would never be able to do again. My eyes still get tired, but I can handle this. I am so thankful for the opportunity to participate in this study. I hope the committee will recommend approval of teprotumumab so that others who suffer from thyroid eye disease can benefit. Thank you for your time and expertise.

DR. CHODOSH: Thank you so much.

Will speaker number 8 step up, introduce yourself, your name and any organization you're representing, for the record, please? Thank you.

MS. BACHMAN: Judy Bachman, and I'd like to thank the National Organization of Rare Disorders for supporting my travel. I am a retired library assistant from Portland public school system, and I live with my husband Paul. I'm a mother of two adult children and the mother of two grandchildren.

I am here today to share my experiences with TED, an autoimmune disease, and how it affected my life, and how participating in phase 2 of the experimental treatment that I received from the Casey Eye clinic at the Oregon Health Science Center University gave me back my normal life.

I was diagnosed with hyperthyroidism in November of 2014. My endocrinologist said that if I experienced eye problems, I should see my eye doctor. By February of the next year, I started experiencing visual problems. It seemed to have happened overnight. My eyes are protruding and they become misaligned. I was seeing double and could not focus on objects.

I was horrified to learn that this is a permanent condition and would become worse as the

tissues behind the eye swelled, and possibly lead to blindness. There was no known cure. I would just have to wait until the disease had run its course to see how much damage had occurred. I knew corrective surgery was often not successful, and I gradually became depressed.

Looking back, there are many ways that TED affected my daily life. At night, I needed to wear a sleep mask to keep my eyes closed while I slept. I used eye drops during the day to keep my eyes moist and less irritated. I slowly stopped reading because I couldn't track the words on the page. Trying to match up words and notes on a sheet of music became especially difficult. I stopped sewing because I couldn't see where the needle of the machine was going, and threading the needle became impossible.

Lights from oncoming cars caused pain to my eyes at night, so I stopped driving, and eventually I stopped driving altogether, relying on others for transportation. Even walking outside took extra care, and outside I would wear sunglasses even in

the shade. Occasionally, I would experience shooting pains in my eyes or an aching behind my eyes. I avoided having my picture taken as much as possible.

Since retiring, my husband and I would often go on 40-mile bike rides and participate in the Cycle Oregon Weekend. None of this happened for me that year. Trying to focus on a bike trail and moving at speeds up to 30 miles an hour just wasn't safe. Even if I had been employed during that time, I would have had to either taken a leave of absence or quit because I couldn't perform my duties. I avoided people I didn't know, looking away or down at the floor. I felt like I was being stared at, bizarre looking. I knew from past experience how I felt when I looked at a person with thyroid eye disease.

When I saw Dr. Gregory Louis, my eye care doctor in March of 2015, he told me about a drug study at OHSU, and put me in contact with Dr. Roger Dailey. I was given a packet of information about the drug study, and I read it several times and

discussed it with family and friends and my husband. I shared it with four medical specialists that I had been seeing.

I decided to enter the trial, and towards the end of the infusions, the condition of my eyes started to look more normal. Visually, things started to improve. My ability to focus on materials improved. My eyes changed so much that I was prescribed new lenses in September that had less of a prism correction. Because of this medication, my eyes never progressed to the point that I would have to consider eye surgery.

I now read without eye strain. I read the notes and words on a sheet of music. Threading a needle is a simple task. Walking over uneven ground is no longer a challenge. Running with the grandkids and hiking is back on the list, and driving is no longer an issue.

I returned to biking the following spring. It was a real treat when my husband and I went snorkeling in late fall of 2016, and I wear contacts without a prism correction. I can take

pictures and focus through the lens of a camera. Next summer, we're going on a 7-day bike trip, and none of this would've been possible without this treatment.

This treatment was a godsend for me. To be anywhere near a city where this experimental treatment was taking place, to have an eye care doctor who was aware of the study, and to be at the stage of the disease that qualified me for this study and to be accepted, even though there was only a 50/50 chance that I received the actual drug and that it would be effective, the odds of all this coming together seems phenomenal to me, and I strongly encourage the FDA to approve this medication so that other people with the disease can have the opportunity. Thank you.

DR. CHODOSH: Thank you.

Will speaker number 9 step up, introduce yourself, your name, and any organization you're representing for the record, please?

MR. RUTTA: Good afternoon. My name is Randall Rutta, and I'm here as president and CEO of

AARDA, the American Autoimmune Related Diseases Association. Like so many others that have spoken to you this afternoon, I am excited that you're considering this very important breakthrough medicine to bring forward and want to talk to you a little bit about some of the experiences that we've identified that very much echo what you've heard; and then the context in which a new medicine like this can come forward and why it's so important to expedite that decision; move forward favorably; and have the support of the broader community to ensure that patients get access to this important medicine.

AARDA is a nonprofit voluntary health agency dedicated to the eradication of autoimmune diseases and the alleviation of suffering due to the negative consequences of their disease and the socioeconomic impact that is often negative and debilitating. Some nearly 50 million Americans experience autoimmune diseases. They and their families are absolutely affected by those diseases, including thyroid eye disease, Graves' disease, and

others. There are some 130 identified autoimmune diseases.

Founded 28 years ago, AARDA remains the only national organization promoting awareness and action across the entire spectrum of autoimmune diseases. It's a category of conditions, as I say, affecting women significantly more than men. It's a leading cause of death, but more likely, it's a cause of discomfort and debilitating circumstances over the course of a normal lifespan.

AARDA, like LADA and other organizations that are here in this room, collaborates with a broad range of expertise and support, individuals, research facilities, government agencies, academic programs, and certainly innovative companies like and including Horizon. We're pleased to have that broad stakeholder interest and support to draw from as we advance the interest of persons with autoimmune diseases, their practitioners, and their communities.

AARDA promotes patient-focused education and services, public awareness, research and advocacy

on public policies, and private sector practices that affect access to medicines and care. We advocate on behalf of patients across the entire healthcare ecosystem. We appreciate the critical role of FDA in advancing patient health. AARDA encourages the FDA to expedite completion of this biologic license application for teprotumumab solution to treat active thyroid eye disease. Every day matters for tens of thousands of people struggling with these diseases, as you've heard already today.

In advance of this hearing, on behalf of AARDA, I reached out to a network of thousands of individuals with autoimmune disease, including those with thyroid eye disease and Graves' disease, and other conditions where they're looking to exactly this kind of solution, this breakthrough strategy, with hope. We heard from people whose lives have been dramatically and negatively affected due to the lack of acceptable non-surgical treatments that have been out there for a long period of time, and you heard some of those side

effects described here already this afternoon.

So I'm here to share with you some of those observations, some of the direct messages that these individuals wanted me to bring to you on their behalf when they came to understand that not only was I here meeting with you, but meeting with you about something that they're all very hopeful about.

We're looking at these innovative medicines that will truly change people's lives for the better, and we want to provide proactive education and support through the FDA and through others to make sure that people do indeed hear about this option and our position to benefit from it. AARDA certainly looks to the FDA to do its part, and you can count on us as a committed partner to ours.

So let me start by just sharing some of these stories. This is a story, not a story of perspective, brought to me by an individual named Seth. Seth could easily be here among us and be testifying with you today. He's a person with thyroid eye disease. He responded to our

invitation to share, and through me, his thoughts on FDA's consideration of this application.

In his words, "At the age of 30, my appearance slowly morphed due to TED. My moderate case of TED, the proptosis I experienced, was coupled with dry eyes that left me red and bloodshot. Where did the person I become to identify with go? How long will this last? Is this permanent?" There really were no answers for Seth.

"I'll never forget when I attended a function, someone asked me if I was high on marijuana, and I was sober. My self-confidence plummeted during this time. I was constantly hidden behind glasses or sunglasses. After two years of waiting for the active phase of this disease to pass, again, because this particular medication was not available at that point in time, I opted for orbital decompression. This improved my appearance, however, I still miss the old me. If the eyes are the windows to the soul, then TED is a soul crusher." That phrase really resonates

with me. And he goes on to say "the FDA should keep an open mind when considering treatments for TED."

So Ted is a soul crusher. I think that's what we've been hearing. It's chilling, it's unfortunate, and perhaps now it doesn't need to be the case. The reality for Seth, it's what it is. For those of us that might be in a position to help people access what's nothing short of a miraculous possible new treatment, that's an exciting place to be. Moving forward with this application in this new treatment is something of a way out.

I stepped into this role at AARDA not that long ago. I've known AARDA my entire career. It's been in health care. I've been very interested in the work that AARDA has done, but in stepping forward as president and CEO, it was exactly because of the opportunities we have and that's under consideration in this room today. We are at a position to look at breakthrough ways in which to help people lead full, active, and healthy lives.

It became clear to me that advancements in

these biologics and advancements in exactly this area, were key. People with autoimmune diseases typically live a long life, but often these lives are severely compromised by debilitating symptoms of their diseases and the side effects of available treatments. I understand truly the effect of treatment that this is, and it's more than just life changing. I believe it truly is life saving. From the responses we received, I selected a few comments that I think really bring this point home.

Carrie indicated that -- her comment to you, "Very severe and disfiguring; a sight-threatening disease. You have no idea what it's like. You can spare others the emotional damage."

Amanda, "We are losing everything due to lack of treatment options, misdiagnosis, and the failure of government to recognize that these conditions are causing permanent disability."

And Gabriel, "The diseases have taken so much from me. I continue to fight it, even so with horrible eyesight, bulging eyes, no thyroid, and only 80 percent of my stomach; yet I finished third

in the New York city marathon in November. Please help get this medicine over the finish line and help bring people hope and the nonsurgical option we need."

These are the voices of patients who reached out through AARDA's network to speak directly to you. What I would also add to their voice -- and it's so compelling -- is that any change that we're able to advance here is going to be done in a context or a framework of how people actually access those medicines.

AARDA commends Horizon Pharma and other companies that are actively seeking innovative treatments and cures. We applaud them, and the FDA is providing incredible, invaluable guidance, oversight education to assure that such treatments are safe and effective, and we value and support the FDA.

Know that AARDA is committed to ensuring that the framework exists for patients to actually take advantage of such innovative treatments and care in ways that support their health, their

wellbeing, their participation and family, the workplace, and in their communities. AARDA is actively seeking to reduce overly long waits for a diagnosis. That path to diagnosis, and we've been talking about a sense of urgency in terms of the active phase of thyroid eye disease -- well, the typical path to diagnosis for people with autoimmune disease is 3 to 5 to 7 to 10 years.

That's already an extremely long journey, and yet here we are presented with an option that could really help people avoid all of the negative effects of this disease if they know about and have access to this new medicine. If it's approved by you and comes to market, that's going to be key. So know that we're looking to reduce that journey, that path to diagnosis.

We're looking to provide integrated and coordinated care. So many of the people we heard from said I go from specialist to specialist to specialist, and they just can't help me. So one of the things we'll need to do around your work is make sure that practitioners and others understand

that something new and exciting is happening.

As we look to empower patients, it's providing patient understanding and education about their conditions. Once that diagnosis comes forward, they need to know what they can do to address it. So FDA has a role that's been enhanced to support patients in that understanding and engagement in their own health. This is critical, and I would call on you to consider that as the committee thinks how could this exciting breakthrough go from bench to bedside; then also to secure this breakthrough treatment.

So often there are barriers that are built into our current healthcare system that impede even basic healthcare, let alone the kind of healthcare that comes from breakthrough medications, particularly in rare and ultra rare circumstances. So know that AARDA is working very hard to ensure that health plan design and the kinds of considerations that can get in between a physician and the patient and the medicine that they need, particularly in this space, are minimized or

eliminated.

Prior authorization is probably something that works for a lot of people, and so does step therapy. But in the case of people with chronic conditions and serious conditions where there's a sense of urgency, you cannot have these bureaucratic type systems kick in and get in between that patient and access to this care that's so important.

Then lastly, often with new medications, you see that value assessment methodologies that are trying to help society understand what's a good investment in terms of medicine and care fail to actually look at the whole person, become fixated on cost and cost alone, oftentimes using flawed data. So these value assessment methodologies also need to be a part of our longer term strategy. As you finish your work, as I hope this new drug comes to market, these are the things we'll want to be thinking about even now so that you not only are assured that patients will start to benefit from the good work that you're doing, but that it serves

as a model for other discoverers, researchers, companies, and patients themselves as they look to address other medical issues in this way.

For AARDA, I would say a call to action to the FDA has moved forward favorably with this particular medication. As you've heard everyone say, this could be a game changer, a life changer, for people who have an active stage TED. You can create an opportunity for a difference that no patients coming before them have had.

I would also say that I would look to this particular new medication, this breakthrough medication, as something that should be supported in the FDA's education directed toward patients and practitioners. You do not want this tree to fall silently in a forest. You want the entire community to benefit from your good thinking here. That may or may not be the specific purpose of your work, but make sure that you think about that and perhaps make some recommendations accordingly.

Know that AARDA and its associates are going to do everything we can to help bring this really

critical new medication forward; raise awareness among patients, not just of this particular disease, only talking about thyroid eye disease, but create a sense of understanding around autoimmunity and have people start to understand that maybe those symptoms I'm experiencing is something that might be in that autoimmune or maybe even that thyroid disease track, and be able to move forward, because time will be of the essence for everyone. It already is, but for a treatment like this, we don't have time to waste.

Then also know that we'll be promoting access to an innovative medicine like this one, so that people truly can benefit. And as was said earlier, it's not just a benefit to the individual but to their family, their co-workers, their neighbors, and their entire community.

Trisha [ph] was one of the individuals that reached out and asked me to share this with you. She said, "After 14 years of living with Graves' disease," she offers, "nothing really works. I've had a hard time seeing when I wake up. My eyes

protrude to the point that my lids don't close. When I cry, it burns so badly. Looking at me, I look drunk or high all the time. New medicines are needed to be researched, approved, and brought to market to help thousands like me who suffer every day."

With that, I'll just close by saying thank you. Thank you for this opportunity to address the committee. AARDA is very encouraged and very appreciative of your due diligence and leadership on behalf of the health and wellbeing of all Americans, including and especially those with autoimmune disease, and thyroid eye disease, and Graves' disease.

AARDA believes that a breakthrough treatment will be game changing for tens of thousands of individuals with thyroid eye disease and their families, as I mentioned. The promise of this option, of being able to have a nonsurgical, in many cases, disease-stopping, and even symptom-reversing effect is so exciting. I mean, this goes beyond just a medical improvement to

really a societal inspiration.

AARDA urges the committee to act in support of this application. Know that we'll do our best to be partners with you as your process moves forward. We will be responsive and influential within the environment to help ensure that your good work and decisions that are made here directly affect and benefit patients in the long run, so that these individuals have timely and accessible access to this new and exciting breakthrough medication in thyroid eye disease who might otherwise lose so much.

We can't let them lose when this hard work has been done, and when the work that you're doing is one of the last steps in closing that gap. So thank you so much and, really, thank you for the very good work that you do.

DR. CHODOSH: Thank you so much.

Will speaker number 10 step up, introduce yourself, your name, and any organization you're representing, for the record? Thank you.

MS. WILLIAMS: Thank you for letting me

speak. Good afternoon. My name is Karen Williams. I currently live in Atascocita, Texas, just outside of Houston, Texas. The National Organization of Rare Disorders afforded my travel here today. I'm married with two children, and I have two grandchildren. I'm retired as of 2017 from the Texas Department of Criminal Justice after 31 years of service to the state.

I was diagnosed with hypothyroidism and Graves' disease in 2000. I had radio-iodine treatment in November 2000 and began taking Synthroid. In approximately 2012, I noticed a change to the appearance of my right eye. At this time, my eye became tearing, swollen, red, and very painful. I also noticed that I was beginning to develop double vision. While driving, I became scared as I began to see double lights in oncoming traffic, and I could not focus properly on the road.

Within months, I also observed that my eyes were beginning to protrude from its sockets. I became extremely self-conscious of my appearance.

My eye continued to protrude, and I got to the point that I would have to drive wearing an eye patch over my eye to prevent the double vision. I also wore sunglasses when in public. I wore the patch to perform daily routine tasks such as watching television and when I was at work. I also began to wear sunglasses at all times to hide my eye.

I was so self-conscious, I would often refuse to have my picture taken, and I felt that everyone was looking at my eye. Due to working at a male penitentiary, you can only imagine the comments that were made to me regarding my appearance. It was a low blow to my self-esteem.

In 2013, my endocrinologist referred me to Dr. Tang at the University of Houston. Dr. Tang began testing and treating me. I was told that my only option to correct the protrusion of my eyes, if possible, would be drugs and/or surgery. After seeing her for several visits, I was asked if I would be willing to participate in a program to test a new drug treatment for my condition. I met

the requirements to be involved in the phase 1 study group. I did not know at this point if I would get the new drug or I would get the placebo, but I was willing to take the chance.

I began following the regimen of receiving blood tests and transfusions of this new unknown drug. After two months, I began to notice that the swelling was going down and my eyes were beginning to recede. The doctors were taking measurements, and they documented my progress. My double vision seemed to disappear, and my eye began to appear normal.

My double vision ultimately went away. I was so excited I would not have to undergo surgery and began to do more daily activities without the use of the glasses and the patch. I resumed many of the activities that I enjoyed, such as pleasure reading, attending movies, and working on various crafts.

I completed this study program approximately five years ago, and I have had minimal, if any, regression in my sight. I continue to travel and

perform the normal activities that I enjoy. I do so without the stumbling and falling that had previously been occurring. My last visit with Dr. Tang was December 2, 2019. There was no change in my eye measurements.

I'm blessed to have been involved in this study. I would not want anyone to experience the same problems that I had endured, and I pray that this drug is approved for those who find themselves in a similar situation. Thank you very much.

DR. CHODOSH: Thank you.

Our last speaker, speaker number 11, will you step up, please, and introduce yourself? State your name and organization you're representing for the record.

MS. BROWN: Good afternoon. My name is Sara Brown, and I am the director of government affairs for Prevent Blindness. I appreciate the opportunity to be here today to speak on behalf of patients who face conditions like Graves' eye disease or TED.

I'm here as part of a professional role, and

I have no financial disclosures in relation to my presence here today. However, as a representative of a patient advocacy organization, I will disclose that Prevent Blindness conducts its work on patient education in partnership with numerous stakeholders, including Horizon Pharmaceuticals; however, our comments submitted to the committee and delivered here today are related to our mission of representing patients and not as a condition of these partnerships.

Prevent Blindness is a patient advocacy organization and the nation's leading not-for-profit voluntary eye health and safety organization. We represent millions of people across the country who live with vision impairment and eye diseases. As such, we impact millions of people across the age and disease continuum each year through our mission of preventing blindness and preserving sight.

We are grateful to the committee for hosting this meeting to allow ophthalmic professionals and members of the patient community and public to

present information and views on the potential benefits and detriments of this emerging treatment, which will be the first of its kind for TED.

TED, sometimes called Graves' ophthalmology or Graves' eye disease, causes inflammation and swelling of the muscle and fat behind the eye that can cause significant impairment of vision, physical pain, and mental and emotional anguish for the patient. Up to half of patients who live with Graves' disease develop TED.

The consequences of TED include impacts to functional vision such as the ability to focus, double vision, and pain to quality-of-life impacts, including social isolation and the inability to work or function independently, and reduced emotional health based on significant changes to physical appearance.

In the active phase of TED, inflammation of the tissue, muscle, and fat behind the eye causes the eye to push forward and bulge beyond the dimensions of the eye socket. If the eyeball protrudes far enough forward, the eyelids may not

close properly when blinking or sleeping. In addition to extreme discomfort and pain, the cornea is unprotected and susceptible to extreme damage. Functionally, the enlarged muscles and tissues surrounding the eye may affect eye position and movement, leading to double vision. The most severe cases include optic nerve compression, which causes permanent vision loss.

Prevent Blindness strives to prevent avoidable vision loss. Teprotumumab provides a means to that end for TED patients. This treatment offers a new approach for patients who live with TED, with an option to control impacts to vision while managing the additional symptoms of their TED during the active phase of this condition.

Patients who live with Graves' eye disease, or TED, experience resulting thyroid dysfunction and may experience extreme emotional and psychological distress due to the changes in their appearance. Current treatment options within the active phase leave patients with only passive means of observation and treating underlying symptoms.

Impacts to patients while a patient is in the active phase can have considerable consequences to quality of life. Therefore, we do ask that the FDA conduct its due diligence and fully consider this treatment on behalf of patients who live with the devastating impacts of TED. Thank you for the opportunity to speak today.

Clarifying Questions (continued)

DR. CHODOSH: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. We're going to turn our attention to address the task at hand, which is careful consideration of data before the committee, as well as public comments. But before we get to the questions, I think we asked the applicant this morning for answers to some specific questions, and I think Dr. Thompson is prepared to do that.

DR. THOMPSON: Thank you so much. Yes, there were several questions that came up through the presentation and discussion this morning that

we wanted to address. First of those, I was asked the question about response in patients who had received radioactive iodine therapy previously.

As I said before, there were 9 patients in tepro and 9 patients on placebo who had received radioactive iodine therapy, and the -- oh, my slide is not projecting. In any case, all nine of them on teprotumumab achieved a proptosis response and none of the patients on placebo achieved or proptosis response. You can see those data here.

There were a number of discussion points about diagnosis and about severity and activity of disease. I'd like to ask Dr. Douglas, and then Dr. Dailey, to come up and briefly comment on those points.

DR. DOUGLAS: The committee had several questions about the diagnosis of active disease and, really, this is a spectrum of findings with active disease. You saw a clinical activity score but, really, this takes clinical experience, and you heard this from the patients. Sometimes this is an inflammatory process where the clinical score

is very high, but also clinically, as we see it, sometimes the inflammation can be rather low, but they have progressive disease with progressive proptosis or severe pain.

So really, it takes quite a bit of clinical experience in a real-world phenomena to know this, but it's kind of one of those things. As an experienced thyroid eye disease specialist, you know very well when you see it, and you also have to discuss the risks and benefits of therapy with patients, based upon the severity of their disease.

Some patients will have pain so severe that they're taking opioids, so you discuss the risks and benefits of what we have right now, which is high-dose glucocorticoids. The last study that was done by the Europeans, two patients died after high-dose corticosteroids. So for many of those patients, we have a very frank risk and benefit discussion based upon what symptoms and severity they're having.

So I think that it's just helpful when painting that context of the diagnosis. Really,

when we think of this therapy, it really is kind of a generational therapy, as I think of it, in comparison to what we have, and I think Dr. Dailey can add a bit more to that.

DR. DAILEY: Roger Dailey. I'm a professor of oculofacial plastic surgery at the Casey Eye Institute on the campus of Oregon Health and Sciences University. I was a principal investigator in both the phase 3 and phase 2 studies. I was also a founding member of the eye TED's group.

I think the speakers from the audience put things in perspective for you. You've seen the group that didn't have the availability of teprotumumab, and they went on to suffer decades of problems. Dr. Patterson's well known to our group, so for over 30 years, she's had these problems, where as you heard from the patients who had the teprotumumab, those symptoms and signs sort of melted away.

I can tell you, going back to the phase 2 study, when that first patient came in, at the

6-week visit, their proptosis had pretty much faded. The significant proptosis had pretty much faded away, as well as their inflammation. It was remarkable. I'm not sure who was happier, the patient or myself, but it was a phenomenal change, that in my 36 years of taking care of these patients, I have never seen with any other therapy. So please keep that in mind. Thank you.

DR. THOMPSON: There were three other questions that I'll address very briefly. The first of these was a question about whether there were patients who had muscle spasms that were more significant in study 2 -- rather in OPTIC-X than they had in study 2, to look at the potential for accumulating adverse events with longer exposure. We did have 2 patients in OPTIC-X who had muscle spasms and who also had muscle spasms in study 2. They both had had muscle spasms in study 2, and they were of the same intensity when they recurred in OPTIC-X.

The next question was about the exclusion criterion. Specifically, in the oncology program,

rather, there had been adverse events of anemia and thrombocytopenia seen. Of course, this is not necessarily unexpected in an oncology patient population, however, as a precaution, that was excluded in the studies. In the thyroid eye disease studies, however, we've seen no clinically meaningful thrombocytopenia or anemia. We have removed this exclusion criterion from OPTIC-X, and we'll be removing it from any future studies we perform.

Finally, there was a question about the overall risk differences for adverse events, and I'm going to ask my colleague Dr. Wiens to come up and address.

DR. WIENS: Brian Wiens. We were asked about risk differences or some way to quantify with the confidence interval the difference in event rates between teprotumumab and placebo. We did provide some very simple normal theory, large sample confidence intervals for the difference in event rates between teprotumumab and placebo.

While we did talk about several different

adverse events this morning, we chose in this slide to focus on the adverse events of special interest. Two of them were not observed in the placebo arm, so we chose not to present confidence intervals. Additionally, I apologize for the typo for diarrhea. The lower bound of the confidence interval should be negative 3.3, not positive 3.3.

DR. CHODOSH: If I might, the significant confidence intervals were for hyperglycemia and muscle spasms; is that correct?

DR. WIENS: Those confidence intervals do not include zero; that's correct.

Questions to the Committee and Discussion

DR. CHODOSH: Thank you so much. Okay, appreciate it.

So we're now going to proceed with questions to the committee, and I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

We have several questions. I'd like to

encourage the entire committee, voting and non-voting, to participate in this part of the meeting. We will have a voting question later. There are some questions that are really just there for discussion, not for a particular vote.

When we get to the voting question, we'll be using an electronic voting system. Once we begin the vote, buttons will start flashing. I'm not really sure what that's going to look like, but we'll figure it out, and they'll continue to flash until you have entered your vote, and even after you've entered your vote. So even though you think it's not taken your vote, it will have, as long as you press firmly.

Please press the button firmly that corresponds to your vote. If you're unsure or you wish to change your vote, you can press the corresponding button until the vote is closed. After everyone has completed their vote, it will be locked in, and it will be displayed on the screen.

Jay will read the vote from the screen into the record, and then we'll go around the room, and

each individual who voted -- again voting members only -- will state their name and vote into the record verbally. You can also say why you voted, if you want to.

We're going to continue through the questions until they're all discussed. I think for those of you in the meeting, several pages back in your booklet, there's a list of the questions. I'm going to read each question, and then you have an opportunity to ask if there's confusion about what the question is or about the wording of the question before we start actually discussing the content or the response.

The first one for discussion -- not for voting, for discussion -- was please discuss the expected onset and duration of effect following the administration of teprotumumab. Please also include in your discussion whether there is a potential safety concern with repeated courses of treatment.

Are there any questions about the intent or the wording of this question?

(No response.)

DR. CHODOSH: Not seeing any, we can proceed on to discussion, and Jay is going to help me by identifying who's next. I think Dr. Burman is called on.

DR. BURMAN: Thank you. Ken Burman. I think this is a relatively straightforward question or comment. What we have to rely on are the studies, and the studies showed that the onset was within 6 weeks and lasted in about 60 percent of patients for 72 weeks.

So I don't think you can say anything more about that or longer duration, and you can't say anything definitively about repeating the infusions, all 7 infusions, because it wasn't done. So I think we have to stick with the data from the studies.

DR. CHODOSH: Dr. Murray?

DR. MURRAY: I'd only modify that comment by saying that the onset can be as early as 6 weeks, but there were patients that had response after several courses of therapy. So I think the onset

can be variable. Then I think the comment about potential safety concerns with repeated courses of treatment, I think we've discussed that there may be potential safety concerns, but the data available to us is relatively limited in that setting.

DR. CHODOSH: Go ahead, Dr. Brittain.

DR. BRITTAIN: I agree with everything that's been said. I'll just add that there's at least potential to learn a little bit about the repeated course of treatment with the study that's not completed.

DR. CHODOSH: Dr. Yoo?

DR. YOO: Dave Yoo. This is more of a comment. Remember, the inclusion criteria was for 9 months, and then they followed it for 24 months. That's pretty much the 3-year mark, at which point this thing had burned out. So I don't think there is an intention that you're going to be using this over a lifetime. If it does reactivate, then you probably would. So I just want to put that in context.

DR. CHODOSH: Dr. King?

DR. KING: Tonya King. Along with the question of potential safety concern with repeated courses of treatment, it sounds, based on hearing the stories of the patients in the public open session, that even the potential side effects of therapy that we've learned about don't compare to living with the disease, that sounds much worse than the potential side effects that could occur. This is something, as was mentioned, that we'll learn more from OPTIC-X and any potential long-term studies that can be done after approval.

DR. CHODOSH: If I can comment, I would like to say that the patient testimonies were very important. I think the data on muscle spasms not incurring at an increased rate, as the treatment progresses, is encouraging but can really only be applied to muscle spasms. I retain some concern -- I don't think that this is a quantifying concern -- about the side effects like loss of hearing, which obviously can have profound impact on those who have it.

Some would say that hearing loss is worse than blindness for some populations. So I think we have to keep those in mind. As I said, those aren't necessarily qualifying statements for me in terms of my decision about how to vote later in this meeting, but I think we shouldn't ignore those. I agree with what you said, that, clearly, having this disease is bad, to put it very simply, and it seems that the side effects might be less bad. Let's keep it simple.

Mary? Dr. Hartnett?

DR. HARTNETT: Thank you. I agree with what has been said. I just want to, as a comment, remember that this has only fewer the 90 patients, so I would hope that we continue to learn more and that a lot of effort is put forth to learn more about the potential side effects going forward.

DR. CHODOSH: Dr. Low Wang?

DR. LOW WANG: Thank you. I was so struck, as I think many of us are, by how well this drug works, and I think, of course, the safety database is incredibly limited. I agree with what's been

said about that.

A couple of comments. One is the proposed registry of 200 patients. I don't understand why that's so limited. I really think that needs to be expanded. There's so much we don't know about the safety of this drug. We've already brought up the point about the possibility that this could be disease modifying. It could be disease modifying in a good way, so it could completely change the course of the disease. But we could also be pushing off, so it may not be limited to three years anymore.

So I don't know that we know how this is going to change the path of the disease, and I do think that the question about the potential implications of repeated courses is super important because I do see that that is going to become used that way.

DR. CHODOSH: Dr. Gicheru?

DR. GICHERU: I think some of the information we got from the public was very helpful, and some of those things have been echoed

here. While the sample size is small, there are concerns about safety. Let's remember that even though we talked about some of the adverse effects, let's remember, for a person who has this disease, if it's not treated, there's 100 percent risk of diplopia and that sort of thing, so I think we need to keep that in perspective also.

DR. CHODOSH: Dr. Atillasoy?

DR. ATILLASOY: Just to add on that, I think that the safety concerns can certainly be addressed in labeling. For example, in Section 5, Warnings and Precautions, some of them can be considered. Section 6.1, where you list adverse events from clinical trials, I think that can be addressed.

I actually think in the other direction, there is a concern, in a good way, that we haven't actually seen the full benefit of the product. We talked briefly about week 28, that there continues to be separation. I would think that longer term, the sponsor may be able to demonstrate the additional benefit of longer term therapy. There seems to be some duration, for example, 1 or

2 years, when there's active disease, where you'd envision this could be used long term. So I think there's that additional aspect, which is very exciting.

DR. CHODOSH: To get back to Dr. Low Wang's point about the post-approval monitoring plan of 200 patients, I wondered how that was arrived at and whether that was going to be even close to sufficient to really get at some of these issues. I like to think anything's possible. So is it possible that patients will need repeated courses?

As you, I think, pointed out, it might be disease modifying in the sense of extending that window of opportunity that was cited as being relatively brief of a couple of years. So we don't really know. It's not that I have an idea that it's going to go one way or another, but I wonder whether that study of 200 patients would really capture fully what we'd want to know long term.

Are there any other --

DR. GICHERU: There was a comment earlier about the Rule of Three. Should that number maybe

be closer to 300?

DR. CHODOSH: To stay in order, I think Ms. Schwartzott is going to speak now.

MS. SCHWARTZOTT: No, I'm speaking as the patient here, the patient representative. I watched my mother go through severe thyroid eye disease. I've had thyroid problems and eye issues myself. I understand the risks. I understand that there should probably be post-approval, if it is approved, and study follow up. But the benefits so far outweigh the risks when you consider what these side effects are and what the symptoms are of the condition, and, to me, it's worth it.

I've already taken that risk myself with other drugs and other trials, and I know that I would say 90 percent of patients would take the risk compared to do nothing and live with those symptoms that they were describing.

DR. CHODOSH: Thank you. Dr. Murray?

DR. MURRAY: My only comment was that in the postmarketing, it seems like the opportunity is relatively broad to be able to encourage more

recruitment into that registry. I would think that you'd want a registry of no fewer than 500 patients to allow you to look at that and capture a group that may undergo retreatment, in particular.

DR. CHODOSH: Well, you could probably decide that, statistically speaking, based on not necessarily the Rule of Three, but some other rule.

Are there any other comments? Obviously, all these questions have some overlap to some degree. So if there are no other comments specific to this question, I propose we move on.

Wiley Chambers? Dr. Chambers?

DR. CHAMBERS: Before you move on, the registry is not something that's currently -- the registry was proposed by the company. It has not been discussed with the agency, nor have any potential postmarketing either commitments or requirements been discussed at this point. So they are all potentially still on the table.

If we end up asking for a postmarketing study, one of the points of this question was how important is it to know the actual duration. This

particular study only looked every 6 weeks. Is it important to know what happens at week 30, 36, 52? How well defined do we need to know how long the therapy lasts in your minds? Will it make a clinical difference whether we know it lasts for 6 months, or 12 months, or 18 months, or 4 years?

DR. CHODOSH: I would think yes, but in doing that, I would imagine that your marker, your event, would be need for retreatment, as a critical -- I mean, obviously, you've got proptosis as a marker, but whether you need to haul in 500 or 200, or whatever the number is, patients every 4 weeks, I personally don't think that's really what's needed because the patient with recurrent disease is likely to present and need retreatment or some other treatment.

So I don't know that it has to be all the parameters that were examined throughout the trial, and I think there are certain side effects, and I think at the end of OPTIC-X, you're going to have data on muscle spasms, and maybe you decide that muscle spasms is not a long-term concern, but

hearing loss, for example, change to a diabetic phenotype from a metabolic syndrome phenotype is an important outcome.

I appreciate that patients want to have their symptoms stop and be reversed, but diabetes brings its own set of symptoms that that patient population would also like to see reversed. So we have to be careful about what might be caused by the drug. So I don't know. I would probably scale it way back and not do so many visits at every interval in that kind of study. I think there might be simpler ways to do it, but that's my own personal take on it.

Others? Dr. Atillasoy?

DR. ATILLASOY: Just from experience in various products and vaccines, I think there are ways to address this. As you said, registries typically used for things like pregnancy registries, I would encourage the sponsor and agency to consider other things like observational data. Presuming this product gets approved by the agency at some point, it is not investigational,

and there becomes an issue of how long you can maintain placebo-controlled trials.

So there are other ways with other types of products, including vaccines, where one can do observational studies to get at some of these really key endpoints that you're seeking.

DR. CHODOSH: Other comments?

DR. LOW WANG: Yes. I was actually thinking of, also, just a simpler, long-term, follow-up study with a much greater number of patients. I really think, as I mentioned, 200 is far too low. I don't even know if 500 is enough; possibly even more. I think the concern is we really have no idea, and I think unless we have some type of control to follow up, I don't know that a registry is going to be enough, and I'm worried about the metabolic consequences, cardiovascular.

Here we're talking about an elevated growth hormone state. I know it's very different from acromegaly, but I think we're introducing some risks that we still don't understand. So I think less intensive follow-up, longer time, and more

expanded.

DR. CHODOSH: I've been reminded that I should be stating my name before I speak. This is Dr. Chodosh, and Ms. Schwartzott is next.

MS. SCHWARTZOTT: Jennifer Schwartzott. In the mitochondrial disease community, we have used registries. We've also used surveys, and we've used computer-generated studies that were done, and they were with the same doctors doing the drug trials. Those have been very, very successful in recognizing some of the same questions we're asking on trials for mitochondrial disease.

So that's something you can look at to bring the patients into it because these are some very, very smart patients. They've had to learn because they've had no other choice, and I believe they should have a say in the questions that we're asking. With what comes out in the future for this and what studies are done, they have some good feedback.

DR. CHODOSH: Jim Chodosh. Thank you for that comment. It was great. If there are no other

comments on this question, I'm going to move to the next question for discussion.

I think that's difficult to summarize, but I think the general conclusion of what I heard on that question was that the committee has concern about longer term safety. I didn't hear anyone say that they were concerned that the risks outweighed the benefits of the treatment.

What I heard is we're all curious and worry a bit about what might follow for patients who are treated, even more so for patients that are treated with multiple courses beyond the time of the study, and that we'd like to know what happens with regard to blood sugar, and hearing loss, and the things that may have -- again, it's hard to create a state of quality, but profound of impact on recipients of the treatment in other ways besides their eyes.

What I heard from the committee regarding onset and duration of effect was that we've acknowledged that it was variable, and I don't really think there was anything else about that.

The next question was -- if we could have

the second question on the slide -- please discuss any safety limitations or safety labeling that should result from the relatively small database of patients in this orphan indication for teprotumumab.

I think I'll start. There are some obvious things. There's concern about pregnancy. I think these things are obvious to the FDA, and I think that patients and physicians providing the medication need to be informed about the results of this trial.

These are all obvious things, but I think an important component, if this is approved in the near future, will be acknowledgement of the relatively small number of patients enrolled, so that the caregivers, or the people who are providing the therapy, as well as the patients who are taking it, understand that we may not know everything we'd like to know in the longer term about the drug, so that at least they feel informed of what I think most of us on the committee feel are some gaps, given the short duration of the data

we have in the small numbers.

Dr. Hartnett, please. State your name again.

DR. HARTNETT: Mary Elizabeth Hartnett. I would echo what you say, but specifically, I would think pregnancy tests before each infusion and maybe glucose monitoring after each infusion, and then A1c as recommended by endocrinologists and other expertise.

DR. CHODOSH: Dr. Brittain?

DR. BRITTAIN: I'm not sure if this is the right question to discuss safety in general, but I'm a little disappointed by the size of the safety database, given this isn't that rare a disease if there were 25,000 cases each year. On the other hand, I understand that was essentially the agreement, so I think we have to live with what we have.

I guess it gives me a little pause, some of the results that we see. Like with the SAEs, the ratio was 7 to 1, 7 cases in the treatment groups in the two studies combined versus 1 in placebo.

They're all kind of heterogeneous, so it's hard to know if that means anything, but that 7 to 1 did jump out at me. It certainly seems that most of the adverse events that people have experienced are acceptable, given the benefit they're getting. But again, as others have said, it sounds like they're going to be some patients for whom the risk-benefit isn't there. I guess, again, as others have also said, it would be, because the knowledge is limited, important for patients and physicians to have a clear sense of what's known and what's not known.

DR. CHODOSH: Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. I just wanted to mention that I thought that the information presented was pretty clear in terms of the fact that I think this drug should be avoided or contraindicated in patients with underlying inflammatory bowel disease or colitis.

DR. CHODOSH: Dr. Burman, please again state your name as you start your comment.

DR. BURMAN: Thank you. Ken Burman. I was

going to echo the fact that it shouldn't be used in IBD patients, obviously pregnant patients, and the question arises whether it should be used in acromegalic patients, although it's rare. Maybe the growth hormone wouldn't go up necessarily because it may be more autonomous, but that's an issue to at least consider. And lastly, there's no question there should be glucose monitoring and hemoglobin A1c monitoring.

DR. CHODOSH: Thank you. Others?

(No response.)

DR. CHODOSH: So in summary, we heard the recommendations for glucose monitoring along with hemoglobin A1c; the restriction to non-pregnant and continuous monitoring so that infusions are not given after one becomes pregnant; the suggestion that patients with inflammatory bowel disease might be best served to avoid the treatment; and the additional concern about acromegaly.

I understand that there would never be any data available because one rare disease times the other makes something really rare, so you wouldn't

know, but theoretically, there might be a concern. I wonder how many patients there are with both diseases in the world. Probably very, very few. Any idea?

(No response.)

DR. CHODOSH: Okay. I think Dr. Stamler had a question.

DR. STAMLER: John Stamler. I'm a bit more concerned about hearing loss, and I wonder if we should monitor hearing, perhaps a hearing test, before treatment starts.

DR. CHODOSH: Other comments about that? Yes, Dr. Weng?

DR. WENG: Christina Weng. I agree with that comment. I think that was one of the adverse effects that I really noted; first of all, the stark difference between that and the placebo group. Second, it's much more specific than some of the adverse events that we see with other drugs, like fatigue, that are more generalizable and may not be attributable; so you really can't ignore that difference.

Not to mention that there was a proportion of patients that did not recover, at least during the observation period thus far, who are still dealing with impacts, even though they might be improving. So if there's a potential for irreversible change in one sense, I don't want to trade one sense for another sense, especially one that's very valuable to many people.

DR. CHODOSH: Thank you. Jim Chodosh. I'm going to recognize you, Dr. Chambers, in a second. It is, I think, a fair burden that audiology is a much more complex thing to request of every patient receiving the treatment than a blood test.

Dr. Chambers, can you comment?

DR. CHAMBERS: Wiley Chambers. I'm just playing devil's advocate. What would you do with the information; if you test somebody and they have hearing loss? As we've heard, there is some suggestion that people with thyroid disease may have a higher rate of hearing loss. Certainly as you get older, there are hearing loss issues.

Would you not treat them? Would you treat

them with a less dose? Would you treat them for a shorter period of time? What would you do? I'm concerned about putting things in label if you don't know what to do with it.

DR. CHODOSH: Dr. Weng?

DR. WENG: Christina Weng. I don't know that it would -- I think that's going to be left up to the provider and the patient. What I think is more important is that there is very discrete awareness that is shared with the patient in knowing what risk to take. I think all of us on an individual level are willing to take -- some of us are willing to take more risks than others. Depending on how severe the disease state is, I think that changes whether or not you would be willing to undergo that.

So I don't think it's a matter of monitoring so much as it is with the glucose issue. I think it's a matter of knowing that that's a possibility, so perhaps with the labeling.

DR. CHODOSH: Dr. Chambers?

DR. CHAMBERS: Wiley Chambers. So the usual

way we would do that would be to identify it either in the adverse reaction section of the label or in the precaution warning so that people are aware it's an event that's been associated, at least temporally, with the product, but not necessarily advocate testing or monitoring. But again, you've identified that it's a potential issue, and let the individual patient and physician decide what the appropriate plan is for that patient.

DR. CHODOSH: Dr. Brittain? Identify yourself.

DR. BRITTAIN: Just a quick comment. If the cases were 8 to 0, I think we have to feel pretty confident that that is not a chance finding, even if there's no understanding of why there would be an effect.

DR. CHODOSH: This is Jim Chodosh again. I'm not sure about that because the numbers are still very small, and if you flip a coin 10 times, you might get 8 hits, but I do think it's a major concern.

The question I would have -- I'm thinking

this through as we're talking about it -- would be what would you do with the patient who already has hearing loss, and would you worry about making it worse? I think that possibly the labeling could include extra precautions in patients who are already aware of hearing loss.

We don't know the mechanism. Assuming that it's a real effect, we don't know the mechanism. It would be really helpful to have some idea about the mechanism because, then, maybe we could predict if you had a certain type of hearing loss already, and you already had damage in some way, from a drug, from sound, from whatever the mechanism is and the problem, that you might be more susceptible or less susceptible. Maybe some patients with hearing loss have no risk with the drug and maybe some without hearing loss do.

So we don't really have enough information, but I think in the post-approval marketing phase, if it gets that far, it would be great to have some way to understand this because I think this hearing issue, if it turns out to be a real effect, could

be very important. I'm sure there's something there, some molecular explanation for this, and we'd want to know it at that point because there are many forms of hearing loss, and they have very distinct mechanisms.

We wouldn't want to dump all -- as an example, patients come in all the time and they want to know whether they can take a drug because they have glaucoma, when in reality, 90 percent of those patients have open-angle glaucoma, and the drug is associated with narrowing a glaucoma. So that specificity is important, however it would be decided to take care of that.

Dr. Low Wang had another comment.

DR. LOW WANG: Yes. Cecilia Low Wang. I was also struck by the incidence of hearing loss and muscle spasms. But I think that the question of monitoring versus not and doing baseline hearing tests, I don't know that that would help because we really don't know the time course, and we don't know the cause.

We don't know that if you have some hearing

loss at baseline, does that mean that you're more likely to get more hearing loss or it's more likely to worsen? We really don't know. If you have baseline tinnitus, does that increase your risk? We don't know that either. I think that if we did have those results, I think it would be hard to really use them.

I think just a strong caution on the label. I guess the one argument for patients with preexisting hearing loss is that if you already have some degree of hearing loss and you also get this and develop hearing loss, then you're losing more hearing, potentially. So I think that would be the one precaution there.

I think that from the information that we already have from the trials that have been done, I think those cases of hearing loss can be characterized further to try to answer this, at least preliminarily, and figure out what needs to be set on the label about hearing loss. I don't know that we've heard enough details today about the patients who are on the trial.

DR. CHODOSH: Ms. Schwartzott?

MS. SCHWARTZOTT: Jennifer Schwartzott. I agree that in the post-approval studies, they should follow the hearing loss and the tinnitus. But really, a hearing test is very easy, so to me, that would be a step that I would be willing to take if they did that before we started this treatment. I would not see a problem with that.

DR. CHODOSH: Jim Chodosh. It strikes me that if this drug were approved, there would be centers that would be interested in undertaking independent studies of hearing loss in treated patients, and that that could be done outside of the sponsor's responsibility, and probably would be of interest to independent investigators.

Dr. Murray had a question or a comment.

DR. MURRAY: Just to echo your comment, it seems that requiring hearing testing when we don't understand mechanism is really not appropriate at this point, but it would be nice to understand the mechanisms so that we could better target labeling going forward or better discussion with our

patients.

DR. CHODOSH: I summarized this already, but I will add that I think everybody thinks that hearing loss is potentially important. There were some differences of opinion in how that should be addressed. Whether it should be mandatory testing before the drug is given, I think was a minority opinion. But I think the majority felt that at some level, hearing should be studied, but whether that's the responsibility of the sponsor or the FDA, I didn't hear a consensus for that.

We're going to go to the next question. This is question number 3 for discussion. Please discuss whether the term "active" as used in the proposed indication is informative to clinicians and patients considering use of the product. I don't think we have questions about the wording, so we'll take comments from the committee.

Dr. Burman?

DR. BURMAN: Thank you. Ken Burman. The Clinical Activity Score, which I'm looking at now, takes into account symptoms, signs of eyelids, and

chemosis and inflammation, as well as changes related to proptosis, and eye movement, and acuity. So it includes signs and symptoms, and actually objective changes. I think despite the fact that it's not a perfect tool, I couldn't think of a better tool to use than the CAS score of 4 or more that they used in these studies, probably plus proptosis, but proptosis can occur without a high CAS.

DR. CHODOSH: Jim Chodosh. Dr. Burman, the way things seem to work in the real world is if that's in the label, then the insurers won't pay for this drug unless you hit a 4. I wonder whether that's a barrier that the FDA really wants to place on the drug. I do think that if the FDA decides that this drug, its benefits outweigh its risks and decides to approve it, I think the physicians who treat thyroid eye disease, generally, as it was said earlier, know active disease when they see it.

So my personal feedback, as I'd like to have as much granularity, I shared the FDA's concern that the scale, like many scales, could be very

misleading in the equal assignment of points to each of these things. Whether you have a little redness at the plica or the seminlunar fold, I don't know what that means, and probably if I pulled 50-plus year olds off the street, I could identify redness in over 50 percent of them.

So I didn't find some of those aspects of the scoring system to be particularly of use. It has to do with my personal bias about these sort of scoring systems, so I'll admit to that.

Dr. Burman?

DR. BURMAN: Thank you. I certainly agree and respect your opinion tremendously, but it becomes so difficult because not every physician has the expertise of the ophthalmologists on the panel, and they may want to use the drugs for very mild erythema that wouldn't be useful and certainly isn't backed up by the studies. So it's a very difficult question.

DR. CHODOSH: Dr. Chambers, can you comment on what the role of the FDA is when a medicine is approved, then it's available to physicians? And

they can even use it off label. I mean, it's an approved medication. It's the right of the physician to prescribe the medication. To what degree is FDA concerned that this definition is going to create, for example, an overuse of the medicine? Which I imagine that is the concern, but please elaborate if you can.

DR. CHAMBERS: Wiley Chambers. The label does define what the product is specifically approved for, so that's what the benefits that outweigh the risks are considered to have been demonstrated for. The agency can, as I said earlier, expand what was done in the clinical trials if they think that's a reasonable expansion to that.

While physicians can use products if they believe it is in the patient's best -- use approved products for conditions that they think are in the patient's best interest, and that's considered the practice of medicine, the reality, as you pointed out, is there is also a payment issue. If it is impossible to get reimbursement for a particular

product, it ultimately affects the availability to patients. While it is not directly the agency's call on whether payment systems choose to go and pay for things, it's part of the reality.

So we like the indications to be as accurate as possible, reflecting what we think the trials demonstrated, particularly any time there is potential confusion. And speaking for myself, I think the term "active" is not well understood by most clinicians that are likely to prescribe the medication. I think that's a potential problem. So in my opinion, we either better define it or remove the term.

DR. CHODOSH: Jim Chodosh. I take prerogative again. Active, I agree. Diplopia when you have it is active, right? Even the chronic so-called burnt-out phases of the disease to the patient is active. I said this before in the morning session. For the patient, when you have double vision, as long as you have it, it's active, so we do have, I think, an issue there.

I think, as opposed to using a score, we

could probably create a list, or you could create a list, of terms that define the things that specialists who see this disease would say is active; proptosis, which is defined by a certain -- and I appreciate the comment you made early, Dr. Gicheru. But it's defined by a certain number of millimeters or asymmetry between the two eyes; exposure; keratopathy; lagophthalmos, inability to close the eyes because of forward movement of the eyes; restriction of eye movements because of this disease process.

I would imagine that an insurer, for example, would want a scan to know that it, in fact, is thyroid eye disease; again, one of the comments you had, Dr. Burman, earlier about is proptosis really the measure? I think it's feasible to do the way -- an ophthalmologist would typically say this is in the active phase, as opposed to using active in a more generic way, to say the patient has symptoms, because we know the symptoms don't go away if the disease is not treated.

I'd like to turn to Ms. Schwartzott.

MS. SCHWARTZOTT: Now, my suggestion would be to use and/or because not all patients -- like my mother had the bulging eyes, but her severe symptoms were more along that CAS score. So I would hate to see us only say for use for proptosis and exclude those other patients. So maybe the and/or would be the answer.

DR. CHODOSH: Thank you. I was suggesting a list, not a single measure. Dr. Hartnett?

DR. HARTNETT: Thank you. Mary Elizabeth Hartnett. I was going to suggest -- and I want feedback -- something like diagnosis of thyroid eye disease with a change in proptosis because that seems to be what the study used as a greater than 2 millimeters proptosis. I believe it was a change over time. That was described earlier, so I was going to suggest that as a potential activity definition.

DR. CHODOSH: Dr. Chambers?

DR. CHAMBERS: Wiley Chambers. The inclusion criteria did not have a change in

proptosis. The success was a change in proptosis, but you didn't have a baseline and then get followed for some period of time. So you don't know -- and again, if you want a change, then you've got to wait some period of time to see the change.

DR. CHODOSH: Did you want to respond, Dr. Hartnett?

DR. HARTNETT: Thank you for clarification. There was a discussion about change in proptosis. The definition of thyroid eye disease plus recent change might be considered as a definition.

DR. CHODOSH: Jim Chodosh. The patient comes in and tells you they've had a change in their eye appearance, so that to me would qualify. If I see a patient with shingles, I don't actually have to see the rash. If they describe an appropriate rash that could only have been shingles, then I know that they had shingles, just to get at that point.

Dr. Yoo?

DR. YOO: Dave Yoo. I guess this is a

question for Dr. Chambers. Dr. Douglas was talking about how this is a spectrum of disease. If you look at study 2, they talk about the different inclusion criteria, including the CAS score, moderate to severe active TED with lid retraction, et cetera, et cetera, plus being euthyroid. The reality is that -- for instance, I've used rituximab off label for treating some of these patients.

Can you say that the recommendation is that this drug is used in conjunction with an ophthalmologist and an endocrinologist, so you limit who uses it? Because the reality is, if the specialists are ophthalmologists and ocuoloplastics, they have to be a vital part of the team that's making the diagnosis in the first place.

DR. CHODOSH: Dr. Chambers?

DR. CHAMBERS: Wiley Chambers. There are restricted programs where we have restricted products to particular physicians deemed to have sufficient knowledge and training, documented

knowledge and training, to be able to give a particular product. That's not typical of this type of product. There has to be some reason to restricting it to people with that particular knowledge and training. That said, it would be more common to try and describe the particular settings that we believe the product is likely to be beneficial in, such that the benefits outweigh the risks.

DR. CHODOSH: Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. To me, I think that actually the duration of eye finding is the most important. For both of these studies, study 1 and study 2, I think patients needed to have been diagnosed with the thyroid eye disease within the past 9 months. I feel like the specific eye finding itself, we're thinking this is probably modifying inflammation. It's maybe anti-inflammatory. We can only change what's reversible, not what's irreversible. I think that some of these findings, we don't know at what point it's become irreversible.

So I feel like there's some time component here, and I don't know exactly what the right one is. We've got lots of experts here, but I think it really has to be the finding itself as well as the duration; so how long has it been around.

DR. CHODOSH: Dr. Atillasoy?

DR. ATILLASOY: Ercem Atillasoy. A few ways to get at some of these issues, first, within Section 14, the clinical study section, the agency can obviously describe some of these elements from the CAS. That can be readily described. I think that'd be very informative. I think the duration, the time to diagnosis, and these aspects you can bring into Section 14.

In terms of the issue of active, I was looking at some other labels. You do obviously have precedent when you look at other products like infliximab. There's language in the indication, for example, for Crohn's disease with active Crohn's disease or severe active. So there is precedent for use of the terminology "active" if that's beneficial. I think things like that, since

you have precedent, it seems like that would be very helpful to have within this label as opposed to a more broad TED.

DR. CHODOSH: Dr. Chambers?

DR. CHAMBERS: Wiley Chambers. My issue with active is not that we can't use the term "active," it's will people understand what you mean by the term "active." Dr. Chodosh mentioned if you have diplopia, as long as you have diplopia, you're going to think the disease is active for you.

DR. ATILLASOY: Right. So I guess the only other way that it would throw forward is the panel's discussed terms such as patients displaying signs and symptoms of TED, then, if you can't find a way to define it. But I would actually include the terminology, signs and symptoms of TED.

DR. CHODOSH: Jim Chodosh. One of the ways to deal with that would be to say if the patient has onset of A, B, and C, within a certain amount of time, then it's considered active, and that would give the physician some latitude to use the medication without being unfairly restricted.

There are patients that might be on the edge, but they have symptoms that are affecting their life and want to use the agent. That might be another way around it.

I think, as I said, a list of symptoms that would correlate with active could be generated; the use of the word "active" with some definitions of things that can represent activity; and then within a certain amount of time from either onset or with recent worsening. And again, "recent" is a general term, not very specific, but you could put a time on it with some extra latitude so we wouldn't restrict it too closely.

I would say for the hearing loss, I think that with these few numbers, we really don't know about benefit even a bit later into the disease. We're making some assumptions based on our knowledge of disease pathophysiology, but sometimes we have surprises. We don't know whether patients at one year out would have benefited or even 18 months or more.

I don't know what that time should be,

Dr. Chambers, and I know that's what you're hoping we're going to tell you. Sorry. Maybe we should all go home now without our dinner. But I think we're getting closer to active than we were when we started this discussion.

If I can summarize then, you're on your own.

(Laughter.)

DR. CHODOSH: No, that's not really how I want to summarize it. If I can summarize, I think that the overall consensus would be that active is a reasonable term to use, but that there should be some qualifiers of what activity means. Those qualifiers should include signs and symptoms that are specific to what an oculoplastic specialist would call active disease. They should be terms that an endocrinologist can also understand and apply; not necessarily best corrected visual acuity, for example, or degrees of diplopia, so that they could also know when these patients would need to be seen.

There could be criteria for measurements such as Hertel measurements, and then a time frame.

I'm open to discussion about the time frame. I would rather it not be 9 months because I suspect that if it worked as well at 9 months, it's still going to work for patients in times after that, but I really don't know how far out to put it. I'd be tempted to put an 18 month or 2 year personally, but I don't know whether that's reasonable for definition of active, and maybe one of the oculoplastic colleagues might have some opinion. You may need to query the oculoplastic community further to determine what they think the window should be.

Dr. Yoo?

DR. YOO: Dave Yoo. I think 18 months to 2 years would be reasonable, and I think if you were to query the ASOPRS and other oculoplastic surgeons that deal with this, they'd probably get a good idea of what that time course should be. But that sounds reasonable to me.

DR. CHODOSH: Dr. Weng?

DR. WENG: Yes, I agree. I think what you said sounds really reasonable. The hard part about

this question is that we are held to what was studied in this small study. I'm in favor of using the word "active" because I think you do have to think about realistically payment issues down the line, et cetera, and you can't have it just something that we're using for very mild cases that don't meet even close to this criteria.

I would stay away from specifics like the CAS or the 9 months that were used in the trial just because, first of all, when you talk about time from diagnosis, that can be really affected, depending on when the patient actually is diagnosed. The same thing with things like diabetes. They could have had it for an extra year or two years before they're actually found out to have it.

Then not to mention, for a disease that really has no other alternative treatment right now, I just think about if it was my family who had a CAS score of 3 and had been diagnosed 10 months and now doesn't qualify for this drug, that would be really devastating. So I agree with what's been

said. I think qualifiers and putting some trust in the professional who's treating this patient to use their discretion and what's going to be best for the patient, I think that's really important.

DR. CHODOSH: We're going to take one last comment before a break. Dr. Stamler?

DR. STAMLER: John Stamler. I generally agree with everything that's been said. I think I would be cautious to restrict clinicians too much with these. I agree with Dr. Weng. Patients, at least in my practice, if I was to ask them, well, when did this start, I'm not sure they would give me a day, like it was on Tuesday on May 5th. It would be, "Well, a couple years ago, maybe," maybe more or maybe less.

I don't think we're going to get a real accurate time scale because it can come on very gradually and slowly. Patients we've heard from, it seemed to be sudden, but in my experience, a lot of patients, it snuck on them, and gradually over time. So putting a specific time, I'd be hesitant to do that. That's my one comment.

The other is I could see this being used in, for want of a better term, patients who relapse. If they had good response, but then two years later, they come back, well, my double vision's back, my eyes are bulging out again, you may want to retreat them. So is that active or not? It's past the time period. The CAS score may be low, but they've got return of their double vision. That may be an issue as well.

DR. CHODOSH: I personally would call that active.

We're going to take a break until 2:45 and resume with the next question.

(Whereupon, at 2:37 p.m., a recess was taken.)

DR. CHODOSH: Jim Chodosh here. We're going to start on the next question of discussion, which is please discuss the need for glucose monitoring after initiation of teprotumumab administration. If needed, please discuss the recommended timing of any monitoring.

Dr. Low Wang?

DR. LOW WANG: I'll start. Cecilia Low Wang. Again, I don't feel that we have enough information to really answer this question. I think that probably, at a minimum, we should have baseline fasting glucose and A1c. There were some patients that it looked like maybe more than half of patients developed hyperglycemia who had baseline diabetes or impaired glucose tolerance, but then there were also patients who had no such history, who also developed hyperglycemia.

So I think we don't know, and I don't think that there is enough detail provided to really be able to answer that, but I think that baseline testing and then probably periodic monitoring after that.

DR. CHODOSH: Other comments? Dr. Burman?

DR. BURMAN: As another endocrinologist on the panel, I just wanted to officially agree with those comments.

(Laughter.)

DR. CHODOSH: There must be data or suggestions from the endocrinology point of view as

to when this would be a worry and how often blood glucose should be measured. For example, we're not worried whether it went up yesterday, a little bit. I would ask that the endocrinologists on the panel make some general suggestions about a reasonable schedule of blood glucose monitoring. I realize that we don't have sufficient information to really know the pattern from the existing data, but maybe you could make some general recommendations.

DR. LOW WANG: I think the use of teprotumumab, if this gets approved, would then put the patient in the category of someone at higher risk for developing hyperglycemia; then it would be under that screening program, I guess, which is basically anyone who's at higher risk might get screening once a year or maybe every 6 months.

Every 6 months may be too much. If you're actively getting this -- and this is, again, where I feel like we don't have enough information, but from what I can see, if you're receiving the infusions, then I think having an A1c or glucose monitoring at least every 6 months would be useful.

If you've already stopped, then maybe once a year. So I think you're at risk, but we don't know what the risk looks like.

DR. CHODOSH: Thank you. Jim Chodosh. Diabetics who are on medications routinely are monitored now, and those on insulin are monitored every day, at least once a day. For those patients, I don't know that they need -- there might be awareness to the physician prescribing that that can be a problem and that could be a cause of increased blood glucose. But for those patients who are not being closely monitored because of existing disease, I think that's where the question would really come up.

DR. LOW WANG: Right. Cecilia Low Wang. That's a good point. For patients with preexisting diabetes or impaired glucose tolerance, but especially diabetes, we already know that if you have active hyperthyroidism, that gives you high risk for hyperglycemia. But I think that the patients who entered these trials either had A1c's of less than 9 percent, that was in study 2, or

they had no change in their diabetes therapies for the previous 60 days. That was the criteria for the inclusion for these trials.

I think that as long as in the labeling it's made clear that this can worsen hyperglycemia. I think that's enough, because if you already have diabetes, you're already monitoring, and I think that's frequent enough.

DR. CHODOSH: So for a patient with normal blood glucose and normal hemoglobin and A1c, should they be checked before starting therapy, and at what frequency should they receive monitoring? I'm doing Dr. Chambers job for him now.

DR. LOW WANG: Cecilia Low Wang. Again, this is where we don't have enough information, but I do think that a baseline A1c basting, fasting glucose are needed before starting.

DR. CHODOSH: Any other comments?

Dr. Chambers, would you like to ask for something more?

DR. CHAMBERS: No, that's fine. Thank you.

DR. CHODOSH: In summary, you've heard it

all. We would recommend, then, baseline testing before starting the medication for anyone who's not already known to be at risk for hyperglycemia. For those that are on insulin, testing their blood sugar at least daily, that's a nonissue because they will know. For those patients who are not known to have a glycemic issue, then increased awareness by those providing the medicine.

Personally, although I won't be prescribing this medicine if it's approved, I would want to know more than a year later whether my infused patients had had a hyperglycemic episode. That's my concern about this.

Go ahead.

DR. LOW WANG: I guess one last comment is that if someone is actively receiving infusions, they should probably have more intensive monitoring. I'm not talking about daily blood glucoses or even weekly blood glucoses, but I think that they'll be coming in for infusions every 3 weeks, so probably a fasting glucose at least every couple of months would be recommended.

DR. CHODOSH: Dr. Hartnett?

DR. HARTNETT: Yes. I thought that the industry mentioned that even after the first infusion, there were episodes of hyperglycemia. I wonder if we know exactly when they occurred, and then it would be helpful to know when to actually test.

DR. CHODOSH: Thank you. Jim Chodosh. Dr. Chambers, perhaps a closer perusal of that data would be informing.

The next question of discussion, which I think some of which has been answered, is please discuss your level of concern with the episodes and frequency of reported: A, muscle spasms; B, hypoacusis/loss of hearing; C, diarrhea/inflammatory bowel disease; D, infection rate; E, alopecia.

We can take these in turn. Muscle spasms, any comments? Dr. Hartnett?

DR. HARTNETT: I was concerned about muscle spasms, and I felt there were some areas that I'd like more information. For example, if there was

any sense of if they were associated with reduced hydration, electrolytes, things like that, and whether or not they were severe enough to prevent people from walking or doing their daily activities, exercise.

DR. CHODOSH: Jim Chodosh. I think they characterize them as mild to moderate, and it's my understanding that there were no abnormalities to explain them. That was my reading of the sponsor's report. It didn't appear that spasms had a big impact on patients dropping out of the study, for example, if you want to use one measure.

I think patients would need to know that muscle spasms were associated in the trial with use of the medication, of the agent, so that they know why it's happening. I'm not knowledgeable about the proper management of those beyond supportive measures.

Dr. Chambers?

DR. CHAMBERS: Wiley Chambers. Part of what we're asking in this question is should we place it in the labeling. And when I say should we place it

in the labeling, these events all occurred more frequently; that, basically, there was an imbalance. That would, more or less, automatically put it in the adverse reaction section of the labeling.

The distinction then becomes do any of these warrant going to a warning precaution section as opposed to just listing them in an adverse reaction section; and obviously the higher bar, would any of them potentially preclude approval without finding out more about them? So that's kind of the three levels we'd sort of like to hear about each of them.

DR. CHODOSH: Dr. Hartnett?

DR. HARTNETT: Mary Elizabeth Hartnett. I wasn't so worried about the muscle spasms as to put them in a warning, or the second level. I would just keep them at the first level, that they were more common.

DR. CHODOSH: My sense of the general discussion earlier was that I think the committee agrees that this doesn't need to be elevated. When

patients read the labeling, when they do, and when physicians read it, they note that muscle spasms will occur more commonly in patients on the drug, or did in the trial, than those on the placebo, and I think that's enough. So I'll leave the summary for muscle spasms at that.

Then hyperacusis, loss of hearing, I heard more concern about ongoing, and I personally would elevate it into the second tier that you mentioned because I think people really should and do need to be aware of it.

For example, the prescribing physician I think needs to have a heightened awareness that hearing loss is still this -- again, particularly because we don't have a good characterization of the mechanism, this unknown-unknown, and to be sure to ask patients about it, and that patients who have hearing loss in the family or a preexisting hearing loss should know about this because it might influence their interest in participating in the study.

Again, if you take the extreme example of

someone who's barely active, if you want to use that word, and there's a question about whether they should receive the agent or not, and then they have preexisting hearing loss or a family history of hearing loss, they might say, "You know, maybe the symptoms I'm having are not that bad, and I don't want to take a chance on losing my hearing."

So my personal feeling is that it's potentially important, but we don't have enough information to elevate it to the third level, and I wouldn't do that at this point, personally.

Other comments? Dr. Brittain?

DR. BRITTAIN: I would just say I agree with you.

DR. CHODOSH: Thank you. Ms. Schwartzott?

MS. SCHWARTZOTT: What I will say is that these are things that are on pretty much most of my medications. These are on the list of symptoms, so it's nothing that we're going to be all that surprised at anyway.

DR. CHODOSH: It's a very good point. As a matter of fact, most systemic medications -- I

don't know. I've never done this survey, but I bet if you did, you could find a -- let's put it this way. A high proportion of medications in their labeling mention hearing loss because it's a common thing. So if during any trial a patient developed hearing loss on the drug, it's going to be listed if it's at any significant percentage.

DR. CHAMBERS: Move on.

DR. CHODOSH: Got it. The next one is diarrhea, inflammatory bowel disease. We heard earlier -- I think it was Dr. Burman who suggested that patients with inflammatory bowel disease not receive the therapy or perhaps that there should be a warning to those patients. I think if you're unlucky enough to have both thyroid eye disease and inflammatory bowel disease, I suspect that there would be a variety of responses.

Patients with inflammatory bowel disease are also miserable when their disease is active, and they might decide to -- again, when you're at the lower threshold of active for your thyroid eye disease, but at the higher threshold of activity

for your inflammatory bowel disease, you might decide maybe I should think twice about taking this medication.

The question I had is to what degree we can rely on the existing data because, like everything else here, we have a limited number of enrollees, and I have to be reminded that with this small number, we don't really know whether this drug is playing a mechanistic role in worsening of bowel symptoms.

Any comments? Dr. Murray?

DR. MURRAY: Dr. Chambers, can you give us the level 3 warning again? All of those clearly hit a level 1, and then we're discussing some meeting to level 2, and then there are some that we may consider for level 3.

DR. CHAMBERS: Wiley Chambers. The level 3, I was saying is it is sufficient concern that you would need to know more information about it before approval.

DR. CHODOSH: Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. I was the

person who mentioned the IBD, so I should be flattered that you mistook me for Dr. Burman. He's a very distinguished endocrinologist.

DR. CHODOSH: You're welcome.

DR. LOW WANG: But just to add to the IBD comment, just looking again about what happened, two of the patients with underlying IBD had exacerbation, and then both got an SAE, and both withdrew. So that seems pretty clear. But then in study 2, patients with that history were excluded, and then we ended up seeing a balanced prevalence of those AEs.

I do think that that should be probably a level 2 warning in my mind. I don't think it's enough to say that we need more data before we approve the drug, et cetera. I don't think that putting it in the list of potential adverse reactions is enough, and I think it should be a warning for the drug.

DR. CHODOSH: Jim Chodosh. Dr. Low Wang, should the presence of inflammatory bowel disease in the patient's history be sufficient to exclude

the patient from receiving this drug?

DR. LOW WANG: Cecilia Low Wang. I think it's the difference between being a warning versus a contraindication. I guess I would say because the safety database is fairly limited. I would probably leave it as a warning and maybe not as a contraindication.

DR. CHODOSH: Jim Chodosh. I agree with that.

Other comments on the committee?

(No response.)

DR. CHODOSH: So to summarize, diarrhea, inflammatory bowel disease, certainly diarrhea would be listed in the list of potential side effects from the studies, but there could be a warning for patients with inflammatory bowel disease about the potential for worsening.

The next question was about infection rate. I'll start. Personally, I found the data confusing. I don't know why urinary tract infections and respiratory infections -- and they seem to be at random sites. I don't know what to

do with that data and what to make out of that, except to probably, again, put it in that tier 1 of increased infections noted in patients.

I also didn't know what to make of the E. coli sepsis patient, and really what that was about. That's concerning, and you always worry that if you get more numbers, will you see more of that? Again, we don't really have a mechanism, I don't think a clear mechanism, for infection, so I'm really interested to hear what the rest of the committee has to say. Don't all speak up at once.

DR. GICHERU: Sidney Gicheru. I believe that was an HIV-positive patient, so should there be something in the labeling about immunocompromised patients? I don't know; just a question.

DR. CHODOSH: Jennifer Schwartzott, please.

MS. SCHWARTZOTT: I would bet that most of those were related to the people's other conditions, just like on the trial I'm in, so I don't know that they're really that much of a cause of concern.

DR. CHODOSH: Well, that is why we do randomized mass clinical trials because there were more events in the treated group than in the placebo group, suggesting that the drug might be conferring an increased risk of infection.

MS. SCHWARTZOTT: It didn't seem very high, though, to me. I'm not a doctor, though.

DR. CHODOSH: Dr. Atillasoy?

DR. ATILLASOY: I was going to say to that point, clearly one could consider applying it into Section 6.1 of the label. The adverse reactions in clinical trials, in aggregate, it is higher in both the sponsor and agency slides, but there's no -- I think so much -- and the next topic, and one who deals routinely with anti-infective products, there's no clear pattern here across bacteria, viruses, fungi, neither those pathogens, nor sites. It's just a very diffused pattern.

DR. CHODOSH: That was the nature of my initiating comment. Thank you. Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. Sorry. I feel like I'm talking a lot, so I apologize.

DR. CHODOSH: That's fine. We're happy to hear you.

DR. LOW WANG: Looking at the sponsor's slides and the incidence of infections, it did look like it was 50 percent higher in the group that received the teprotumumab. So it does look like, at least numerically, that there's this increased risk of infections. I don't know if it's due to the anti-inflammatory effect that we think that IGF-1 inhibition is decreasing inflammation, decreasing cytokine release, et cetera, and if it could be dampening down the overall response that is often appropriate for infections and increasing the risk for worsening infections.

So I don't know if that's the mechanism, but I do think that that's -- I don't think that it necessarily reaches the level of a warning, but I guess -- I don't know how other drugs in this class, other biologics -- my sense is that many biologics seem to increase the risk for infections, and I don't know how we've treated that in terms of warnings versus adverse reactions.

DR. CHODOSH: This is Jim Chodosh. Well, some biologics dramatically increase the risk of infection. For example, infliximab, if you give it to somebody with tuberculosis, even one dose has been associated with death. That's my understanding. This drug clearly doesn't carry that risk, but I agree with your premise.

Dr. Atillasoy?

DR. ATILLASOY: No, I was just going to mention that, absolutely, there are many that carry those types of warnings. Those, though, generally are immunosuppressive in reaction and facilitate deep fungal or other infections. Those are clearly labeled with those warnings.

DR. CHODOSH: Seeing no other comments, to summarize, we think it should be noted so that physicians and patients are aware. It's not really clear that it would modify a treatment course, though. So if you had a urinary tract infection or an upper respiratory tract infection while you're on the medication, it's not clear to me that the clinician should stop or prevent your next infusion

because there's not enough data yet.

Let's go to the last one on this list, alopecia. Dr. Atillasoy?

DR. ATILLASOY: Again, just putting on the dermatologist hat, I would comment that if we had seen patterns of alopecia such as alopecia areata, which is circular, which really is an autoimmune phenomenon, or universal hair loss, alopecia universalis, things like that, then one would posit a mechanism-based reaction.

Other than that, my comment's the same as with item D. You just have this general, nonspecific rate here. Again, it should be listed, and it will be listed I'm sure in Section 6.1, the adverse reactions in clinical trials.

I hate to say this as a dermatologist and one who has some hair challenges myself, but I think weighing everything that we've heard from the company, the experts, the panel, and the eloquent speakers from the public, I do think that this is much less significant, I have to admit, and the benefits really outweigh; so not a very meaningful

rate of alopecia here, but should be listed.

DR. CHODOSH: Jim Chodosh here. Yes, I think we'd all rather be bald than blind. However, it's important for people to know, to have expectations about the medications they're on so that they know that it could -- surprises are not welcome; let's put it that way.

Ms. Schwartzott, did you want to say something?

(Ms. Schwartzott gestures no.)

DR. CHODOSH: Dr. Gicheru?

DR. GICHERU: I was just going to say, as the committee member with the least hair --

(Laughter.)

DR. GICHERU: -- I agree with you.

(Laughter.)

DR. CHODOSH: You agree.

So I think we've summarized each of those, and I don't see any other comments.

The next question is a voting question. I know you're all very excited about that. The question is, do the potential benefits of using

teprotumumab as recommended outweigh the potential risks associated with use of the drug product for the intended population?

It's my understanding that we can discuss this before we vote; is that correct? Does anybody want to make a statement about that? Dr. Murray?

DR. MURRAY: I think the efficacy in an unmet medical need is outstanding for the drug, as we've described, and I think the uncertainty lies with the small patient population and the potential risks. But from the discussion that we've had, I think this is one of the more remarkable drugs coming available to treat unmet need in a rare disease. So I think that it, for me, clearly does meet that threshold.

DR. CHODOSH: Dr. Yoo?

DR. YOO: Dave Yoo. I would agree with that as well. I think that we've been looking in the oculoplastics and endocrinology community for a drug like this, something that is potentially going to be modifying the disease course rather than just treating the issues that develop from the disease.

So remember, even the surgeries can have side effects, so that's another way to look at this. When you do surgeries, patients can get reinflamed. When patients go on high-dose steroids, they can get cytotic [ph] [? cytotoxic] from those as well, and I have patients that are terrified of going back on steroids. So yes, I think it is modifying, and the benefits outweigh the risks.

DR. CHODOSH: I'll comment. As a clinician, I'm a corneal specialist. I do see the corneal complications of thyroid eye disease. I can't say this about every disease that I treat, but I hate this disease. It's a devastating problem for patients. I so appreciate those of you in the audience who spoke earlier for your eloquent descriptions of the impact of this disease on you personally.

This is a disease that we need to do something for, I believe. I'm not necessarily saying in the statement about how I'll vote, I'll get to that later, but this is a bad disease, and

it has a tremendous impact on people's lives. I also think that the data presented, although the numbers were small, was quite remarkable for a clinical trial.

Anyone else want to comment?

(No response.)

DR. CHODOSH: So is it time to vote?

(Dr. Fajiculay indicates yes.)

DR. CHODOSH: At this time, you're going to be asked to press the button on your microphone that corresponds to your vote. You'll have 20 seconds. Press the button firmly; don't break the machine. After you've made your selection, the light may continue to flash again. Again, the question is, do the potential benefits outweigh the risks? So it's yes, no, or abstain. If you're unsure, you can change your vote. Press the corresponding button again, but be quick.

(Voting.)

DR. CHODOSH: It looks like the lights have stopped flashing. Hope you all voted.

DR. FAJICULAY: For the record, the results

are 12 yes; zero no; zero abstain; and zero no vote.

DR. CHODOSH: Everyone has voted. It's now complete. We're going to go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why. I think our first voting member is Dr. Yoo.

DR. YOO: David Yoo. I voted yes. When this drug came out in the New England Journal of Medicine as a phase 2 trial, I was excited about the potential for the disease modification and wanted to really see what the data showed. Despite the conversations about the numbers, I think it has huge promise to change the course of the disease for all these patients with Graves. So I'm very excited about this particular drug.

DR. CHODOSH: Dr. Brittain? Hang on one second, Dr. Brittain.

Dr. Hartnett, I understand you have a flight. You're okay?

DR. HARTNETT: I'm okay until 3:30. I hope we can --

DR. CHODOSH: Okay. We're going to work on it.

DR. FAJICULAY: Start on that side.

DR. CHODOSH: Why don't you go ahead, Dr. Hartnett?

DR. HARTNETT: Mary Elizabeth Hartnett. Yes.

DR. CHODOSH: Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. I voted yes. Are we supposed to comment right now or are we going to do that later?

DR. CHODOSH: You can or you can defer.

DR. LOW WANG: I just wanted to say that I really, really appreciated the perspectives that were expressed in the open public hearing. I thought speaker number 6 and number 8 were very, very eloquent, and I appreciated them speaking out.

I thought the data for the benefits were really, really striking, especially the difference between placebo and the drug. I think there are risks and there's limited safety data, but I think they're manageable, and I think, hopefully, we can

get more data to support the safety.

DR. CHODOSH: Dr. Gicheru?

DR. GICHERU: Sid Gicheru. I voted yes. I really appreciated the comments from the public. I think we're finally going to be able to get a lot of people some help.

DR. CHODOSH: Dr. Burman?

DR. BURMAN: Ken Burman. I voted yes because I believe the potential benefits of teprotumumab outweigh the potential risks and side effects. This agent apparently provides benefits for the thyroid eye patients. Not demonstrated by any previous treatment modality, the seminal question to me, in addition, is whether the indications for treatments should mirror the study inclusion criteria or whether the indication should be slightly broader, based on clinical or physician experience.

My thoughts are mainly to use the study criteria, mainly including the Clinical Activity Score of 4 or more and/or proptosis. However, these indications should be reasonably expanded;

for example, noting duration of eye disease for 12 to 18 months rather than 9 months.

I think CT or MRI studies are used clinically and should be employed in the diagnosis of these patients as well, if possible. Monitoring should include all the side effects that we have mentioned. I agree with the postmarketing studies suggested by the sponsor to include a registry with a number of patients to be decided, appropriate labeling, and support for patient and physician experience. Thank you.

DR. CHODOSH: Thank you. Ms. Schwartzott?

MS. SCHWARTZOTT: Jennifer Schwartzott. I'm very excited for the patient community. This is going to be a life changer, and it offers hope to conditions that were so hard to treat before. I want to thank Horizon Therapeutics for doing this study, and in my opinion, it was a well-designed study and hope for more in the future.

DR. CHODOSH: Thank you. Dr Stamler?

DR. STAMLER: John Stamler. I voted yes. I welcome the addition of this drug to our

armamentarium to treat this horrible, horrible disease and is really maybe the only arrow in our quiver. Thank you, Horizon, for bringing it.

DR. CHODOSH: Dr. King?

DR. KING: Tonya King. I also voted yes. As a statistician, I would generally request for larger studies to be done, but I think this was very convincing. I'm convinced that this is going to be very important to move forward.

As mentioned, additional studies can be done to monitor other side effects post-approval. I also want to thank the members from the public who spoke. I think that was very valuable and important. Thank you.

DR. CHODOSH: Jim Chodosh. I voted yes, and I think you've heard loud and clear why. I again want to thank the members of the community who spoke today.

Dr. Murray?

DR. MURRAY: Timothy Murray. I voted yes also. I want to thank everybody, including the panel members. I thought the discussion was

excellent. The testimony from the at-large members was moving, and it's really a pleasure to participate and seeing a drug being designed and moving forward in the clinical trial for a disease that really has not been treatable for us in the past. So I really applaud everyone involved.

DR. CHODOSH: Dr. Weng?

DR. WENG: Christina Weng. Again, I share similar thoughts of the panel. Thank you so much for sharing your stories. Those were very moving and really helped to remind us of the context we're working in with a terrible disease for which there's really no other alternative treatment that parallels the effects that we're seeing. Yes, we have limited data, but I think that the adverse effects that we've seen, by far, for the vast majority of them, are very manageable.

DR. CHODOSH: Dr. Brittain?

DR. BRITTAIN: Erica Brittain. I voted yes. It was a pretty easy vote, easier than they usually are. I also want to echo what other people have said about how moving the public hearing speakers

were and the great presentation that the sponsor gave. I am concerned about the small database, safety database, and there were certainly issues that were identified, and there may be issues that were not identified because it was small and short term; so that is a concern. But it's pretty clear that the risk-benefit is favorable for a clear majority of the patients and may be highly favorable.

Just a couple things to add that came up before that. I think there probably should be a special study on the hearing in addition to the registry.

DR. CHODOSH: Thank you. We had one more question. I think we've actually hit on this a lot, and we'll have to ask Dr. Chambers what else he wants from us. The question is, if teprotumumab is approved, are there specific recommendations for the labeling.

Dr. Chambers, what's remaining that you want to hear from us about?

DR. CHAMBERS: Wiley Chambers. I just

wanted to make sure there was an opportunity; if there was anything else that people identified as they went through the briefing material or heard in any of the discussion, that they had an opportunity to let us know of things that they thought we should make sure get included in labeling.

DR. CHODOSH: Are there any other comments from the committee?

(No response.)

DR. CHODOSH: Dr. Chambers, I thought the FDA did a fantastic job of helping us to understand the study, and your presentation was very good. I also want to thank the sponsor for a very clear presentation and for their work on this important disease and huge unmet need. The committee members did a fantastic job, and it's really a pleasure and a privilege to be here with you.

I don't see any other comments, but Dr. Chambers, if you have any, please.

DR. CHAMBERS: My only other comment is to again thank everybody for taking the time out of your schedule. We do understand what the

disruption does to people's schedules, including at this time of year. But I want to thank you very much for taking the time to come and help us try and understand this product, and I wish everybody safe travels back.

Adjournment

DR. CHODOSH: So I believe I can speak for the committee that I think we're all pleased that we took the time to do this because to play even a small role in helping to push forward -- again, we understand this is an advisory committee, not a deciding committee, but to the degree that we've helped to push this forward, I personally feel good about the time I took away from my other activities. I'm really, really glad to be here, and I think that's probably similar to everybody else here. Thank you so much. The meeting is adjourned.

I have to read one more thing. Panel members, please take all personal belongings with you, as the room will be cleaned. You can leave your name badge on the table so it can be recycled.

Any other materials left on the table will be disposed of. The meeting is adjourned. Thank you.

(Whereupon, at 3:22 p.m., the meeting was adjourned.)