FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE (AAC) AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Virtual Meeting

Wednesday, March 24, 2021

9:00 a.m. to 4:37 p.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. SUAREZ-ALMAZOR: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email and phone number are currently displayed.

My name is Maria Suarez-Almazor, and I will be chairing this meeting. I will now call the March 24-25, 2021 Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. Dr. Moon Hee Choi is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. CHOI: Good morning. My name is Moon Hee Choi, and I'm the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and your affiliation.

Ms. Johnson?

MS. JOHNSON: Here.

DR. CHOI: Ms. Johnson, can you please state your name for the record and your affiliation, please?

MS. JOHNSON: Hetlena Johnson.

DR. CHOI: Thank you.

Dr. Marek Honczarenko?

DR. HONCZARENKO: Yes. Good morning. Dr. Marek Honczarenko. I'm senior vice president for clinical sciences for GSK, and industry representative, non-voting member of the committee.

DR. CHOI: Dr. Nason?

DR. RICH

DR. NASON: Good morning. This is Martha Nason. I'm a biostatistician at the National Institute of Allergy and Infectious Diseases.

DR. CHOI: Dr. Oliver?

DR. OLIVER: Good morning. I'm Alyce Oliver. I am an adult rheumatologist at the Medical College of Georgia at Augusta University.

DR. CHOI: Dr. Pisetsky?

DR. PISETSKY: Dr. David Pisetsky. I'm a rheumatologist, professor of medicine and immunology, Duke University Medical Center.

DR. CHOI: Dr. Richards?

DR. RICHARDS: Good morning. John Steuart Richards. I'm an adult rheumatologist at the VA Pittsburgh Medical Center and the University of Pittsburgh.

DR. CHOI: Dr. Singh?

DR. SINGH: Good morning. Jasvinder Singh. I'm an adult rheumatologist at the University of Alabama in Birmingham and professor of medicine and epidemiology at the University of Alabama at Birmingham.

DR. CHOI: Dr. Calis?

DR. CALIS: Good morning. I'm Karim Calis. I am director of clinical research and compliance and chair of the Institutional Review Board at NIH, working with the National Institute of Child Health and Human Development.

DR. CHOI: Dr. Griffin?

DR. GRIFFIN: Hi. I'm Dr. Marie

Griffin [audio feedback]. I'm getting a lot of feedback here. I'm a general internist and pharmacoepidemiologist and professor emerita of health policy at Vanderbilt.

DR. CHOI: Dr. Habel?

DR. HABEL: Good morning. This is Dr. Laurel Habel. I'm an epidemiologist at Kaiser Permanente's Division of Research in Northern California.

DR. CHOI: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Good morning. Sonia Hernandez-Diaz, professor of pharmacoepidemiology at the Harvard Chan School of Public Health in Boston.

DR. CHOI: Dr. Hovinga?

DR. HOVINGA: Good morning. I'm Collin Hovinga. I'm an associate professor at University of Texas at Austin, and I'm senior vice president of a public-private partnership called I-ACT for Children.

DR. SUAREZ-ALMAZOR: Dr. Hovinga, we're having a hard time hearing you. Can you hear me

ok?

DR. HOVINGA: Yes. Can you hear me?

(No response.)

DR. HOVINGA: Can you hear me? Hello?

DR. CHOI: Yes. I'm sorry. Would you mind repeating your name and your affiliation? We didn't hear what you were saying.

DR. HOVINGA: I'm Collin Hovinga. I am an associate professor at the University of Texas at Austin. I'm senior vice president for a public-private partnership called I-ACT for Children.

DR. CHOI: Thank you.

Dr. Kulldorff?

DR. KULLDORFF: Good morning. My name is Martin Kulldorff. I'm a biostatistician and epidemiologist, and a professor of medicine at Harvard Medical School's Division of Pharmacoepidemiology.

DR. CHOI: Dr. Meisel?

DR. MEISEL: Good morning. Steve Meisel, director of medication safety for M Health

Fairview, an integrated health system based in Minneapolis.

DR. CHOI: Dr. Nelson?

DR. NELSON: Good morning. I'm Lewis Nelson. I'm chair of the Department of Emergency Medicine and a medical toxicologist from Rutgers New Jersey Medical School in Newark, New Jersey, and a senior consultant to the New Jersey Poison Control Center.

DR. CHOI: Ms. Robotti?

MS. ROBOTTI: Hi. I'm Suzanne Robotti. I'm the president of MedShadow Foundation and the executive director of DES Action USA.

DR. CHOI: Dr. Cheng?

DR. CHENG: Good morning. This is Edward Cheng. I'm an orthopedic surgeon, professor on the faculty at the University of Minnesota in Minneapolis.

DR. CHOI: Dr. Horton?

DR. HORTON: Good morning. Dan Horton, assistant professor of pediatrics and epidemiology at Rutgers University, where I am a pediatric

rheumatologist and pharmacoepidemiologist.

DR. CHOI: Dr. Katz?

DR. KATZ: Good morning. I'm Dr. Lee Katz. I'm a professor emeritus, Department of Radiology and Biomedical Imaging at Yale University School of Medicine in New Haven, Connecticut.

DR. CHOI: Mr. O'Brien?

MR. O'BRIEN: Good morning. I'm Joe O'Brien. I'm president and CEO of the National Scoliosis Foundation, and I am the patient representative.

DR. CHOI: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Good morning again. I'm Maria Suarez-Almazor. I'm a rheumatologist and clinical epidemiologist and professor at the University of Texas, MD Anderson Cancer Center.

DR. CHOI: Dr. Billy Dunn?

DR. B. DUNN: Good morning. I'm Dr. Billy Dunn. I'm the director of the Office of Neuroscience at the FDA.

DR. CHOI: Dr. Bastings?

DR. BASTINGS: Good morning. I'm Dr. Eric

Bastings. I am deputy director of the Office of Neuroscience at the FDA.

DR. CHOI: Dr. Roca:

DR. ROCA: Good morning. My name is Rigo Roca. I'm the director of the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Office of Neuroscience.

DR. CHOI: Dr. Borges?

DR. BORGES: Good morning. I'm Silvana Borges. I'm the acting deputy director for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the office of Neuroscience at FDA.

DR. CHOI: Dr. LaCivita?

DR. LaCIVITA: Good morning. This is Cynthia LaCivita. I'm the director of the Division of Risk Management in the Office of Surveillance and Epidemiology at FDA.

DR. CHOI: Dr. Ho?

(No response.)

DR. CHOI: Dr. Ho, can you hear me?

MR. HO: Yes. This is Martin Ho. I am associate director of the Office of Biostatistics

and Epidemiology from the Center for Biologics Research and Evaluation, presenting on behalf of the Center for drugs Evaluation and Research -- Research and Evaluation. Sorry.

DR. CHOI: Thank you.

DR. SUAREZ-ALMAZOR: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Moon Hee Choi will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management 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 is 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 the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential

financial conflicts of interests of their own as well as those imputed to them, including those of their 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 the discussion of biologic license application, BLA, 761130, tanezumab subcutaneous injection, submitted by Pfizer Inc., for the proposed indication of relief of signs and symptoms of moderate-to-severe osteoarthritis in adult patients for whom use of other analgesics is ineffective or not appropriate.

This is a particular matters meeting during which specific matters related to Pfizer's BLA will be discussed. Based on the agenda for today's meeting and all financial interests supported 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 committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Marek Honczarenko is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Honczarenko's role at this meeting is to represent industry in general and not any particular company. Dr. Honczarenko is employed by GlaxoSmithKline.

With regard to FDA's guest speaker, the agency has determined that the information to be provided by the speaker is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Deborah Marshall has acknowledged that she may hold stock in the company through mutual funds that are managed by a mutual fund advisor.

She is principal investigator and co-investigator on numerous competitor research grants from the Canadian Institutes for Health Research; the Arthritis Society; and the Canadian Rheumatology Association in the area of osteoarthritis.

This will be expected in her role as a professor and the Arthur J.E. Child chair in rheumatology outcomes research. She has not received any funding personally from any of these grants. She also works in a bone and joint health institute within the University of Calgary and she is a member of national networks interested in musculoskeletal health.

Dr. Marshall provides ad hoc consulting services in the area of preferences research on occasion. She has served on numerous boards and committees in the area of arthritis.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal imputed financial interest, the

participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

DR. SUAREZ-ALMAZOR: We will proceed with FDA opening remarks from Dr. Rigoberto Roca, the director of the Division of Anesthesiology, Addiction Medicine, and Pain Medicine.

FDA Opening Remarks – Rigoberto Roca

DR. ROCA: Good morning. This is Dr. Roca. Welcome, chairperson, members of the committee, and invited guests. As you've heard today, we will be discussing the application by Pfizer for tanezumab, and Dr. Choi just read the indication to the panel, and I will not repeat it at this point.

What I would like to do in the next couple of minutes is talk a little bit about setting the stage, what it is that we're hoping to accomplish during this two-day meeting, and then very briefly go over the agenda that was previously shown; and

we can come back to that in a little bit.

Tanezumab is an immunoglobulin G type 2 monoclonal antibody that selectively binds to nerve growth factors. As we know, nerve growth factor is upregulated in response to injury and inflammatory conditions and, based on preclinical data, plays a role in pain signaling by inducing peripheral and central sensitization.

The development program for tanezumab spans more than 15 years. The applicant has conducted 41 clinical trials, 38 of which were interventional. The development program has included clinical holds in an advisory committee in 2012. The review team has concluded that the development program provides substantial evidence of effectiveness, however, the treatment effect size is modest and there is no convincing evidence of a superior efficacy of tanezumab over NSAIDs.

As was described in the background packaging, as will be presented today, two serious toxicities were noted during the drug development program, one of which was the one that resulted in

the clinical hold in the advisory committee; specifically, that would be joint destruction. Neuropathy was also noted, and it is one of the things that is described in the background package, but the main one is the joint destruction.

As previously mentioned, the advisory committee was held in 2012, after which there was a redesign of the development program, where these medication measures were instituted in the programs to try to minimize the effects of tanezumab on joints.

Also in the background package, you will have noted that one of the endpoints was something called composite joint safety endpoint, which included five different radiographic diagnoses that were described in the background package and will be mentioned in the presentations today.

It's important to note that the studies conducted by the applicant after 2015, which we refer to as the post-2015 studies, are the ones that are most relevant to evaluate the risk-benefit of tanezumab and the effectiveness of the risk

mitigation approaches proposed by the applicant, and that is the focus of the agency's review and what was included in this background package.

In addition to the composite joint safety endpoint, it was also noted that tanezumab is associated with an elevated risk of requiring total joint replacement. There was also evidence that tanezumab can target healthy joints. And lastly, it appears that there's a risk for developing joint destruction that is higher when NSAIDs and tanezumab are used concomitantly.

To address some of these issues, the applicant has proposed to market tanezumab with a risk evaluation and mitigation strategy, or REMS, and that is one of the topics that we will ask the advisory committees to consider.

As you go through, there are a couple of things that I would like to have you keep in mind as you listen to the discussion and the presentation, as they form the major portion of the issues that we would like for you to consider. The first one, again, relates to the issue of the

toxicities and adverse events related, and whether the applicant has adequately characterized the risk of the drug's related adverse reactions.

The second one is to consider the risk mitigation strategies that were used in those post-2015 studies, and lastly, whether the REMS being proposed by the applicant can ensure that benefits of tanezumab outweigh its risks.

Let me just go back real briefly to the agenda. It was posted a few minutes ago. What I wanted to note was that -- well, we won't post it up now, but that's fine -- after these remarks, there will be a presentation by the applicant and opportunity for clarification questions. But before the applicant does his presentation, we're going to have a presentation by Dr. Marshall, which was described before.

The reason I want to mention that specifically is because the applicant had included information on a patient preference study, and it is part of the background package that the review division put together. Because of that, we felt it

would be important to have Dr. Marshall do a brief presentation regarding the fundamentals of this area of study.

Then the applicant will do their presentations, there will be clarifying questions, and we will break for lunch. After lunch, FDA will do their presentation, there will be an opportunity for clarification questions, and then we will have a break, having the open public hearing later on this afternoon.

At this point, I would like to turn it back to the chairperson, and we'll continue with the advisory committees. I'd like to thank the committee members and invited guests for your time from your busy schedules to help us work through this application. Thank you very much.

DR. SUAREZ-ALMAZOR: We will proceed now with the guest speaker's presentation from Dr. Deborah Marshall.

DR. D. MARSHALL: Thank you to the chairperson. I just wanted to confirm, Can you hear me. This is Deborah Marshall.

DR. CHOI: Yes, we can hear you.

Guest Speaker Presentation – Deborah Marshall

DR. D. MARSHALL: Lovely.

Good morning to everybody, and thank you for the privilege to provide this brief overview of patient preference information. I'm really delighted to be invited and very excited about these discussions and your deliberations.

This is the overview of a very challenging task that has been given to me today. I'm going to cover these four topics in a very short time. As requested by the FDA, we'll focus on two specific approaches only, the best-worst scaling, Object Case 1, and forced choice, discrete choice experiments, in the context of patients as respondents.

Collecting and using PPI can help support patient centeredness, and PPI can now be considered as part of valid scientific evidence. The scope of what matters to patients goes beyond the key outcomes of measures of safety and efficacy, and what matters to patients can also include other

aspects of interventions such as process measures. As an example, treatments for rheumatoid arthritis vary by mode of administration, so they can have different routes and different frequencies.

How is PPI defined? PPI is qualitative or quantitative assessments of the relative desirability -- that is around the benefits -- or the acceptability -- and that is the harms or risks to patients -- of features that differ amongst the alternatives.

To be clear, PPIs are not patient-reported outcomes or shared decision making. While PROs provide a snapshot of the patient's own assessment of health status at a point in time, they don't reflect how much patients value alternatives. Their decision making on the other hand, of course, is a collaborative process, and it's a collaborative process in which patient values and preferences are considered in addition to the scientific evidence.

For the three types of PPI, there is increasing complexity to this study design and

methods, moving from left to right on this slide. With the first using qualitative methods, we can identify what matters to patients and what aspects of a health service or treatment are priority. With the second, in the middle, we are still identifying priorities but also the order of what matters. And this relative importance is captured using simple quantitative methods.

With the third type, on the right, we measure how much it matters, applying quantitative methods that are designed explicitly to capture trade-offs amongst the attributes, and this will allow measurement of the relative importance, the assessment of benefit-risk trade-offs, and segmentation based on preference heterogeneity. Of course, all of this is conditional on the included attributes and range of attribute levels.

There are multiple methods to elicit and measure PPI, and these are two well-known inventories from the Medical Device Innovation Consortium on the left, and on the right, the Innovative Medicines Initiative, or IMI, PREFER.

And you can see how various PPI methods are grouped.

We will focus only on two stated preference methods. Both use surveys to elicit preferences. BWS Object Case 1 is a ranking method and DCEs are choice-based methods. BWS measures the order of what matters and DCEs measure and quantitate relative importance and trade-offs as marginal rates of substitution.

So now for a few minutes on analysis interpretation of results, BWS object case was the original form of BWS proposed by Flynn and Louviere, proposed as a replacement for traditional methods of the preference measurements where you use ratings or things like the Likert scale. It's comparatively easier than rating tasks, which require a full ranking of all the choices.

Attributes in BWS object case have no levels and choice scenarios differ only in the subset of the attributes that are shown. The number of scenarios required to identify complete ranking depends on the number of attributes.

This is an example of a BWS about non-surgical management for osteoarthritis. In this case, there are 9 attributes, and each choice task includes a subset of 3 attributes. We use an experimental design so that each attribute appears a specified number of times and each pair co-occurs a specified number of times. Then in each choice task, the respondents are asked to indicate a choice of the best or most important attribute and the worst or least important attribute.

These are some example results. Pattern of choices provides the data so that we can estimate the relative importance or ranking of all the attributes. A basic count analysis counts the number of times the attribute is chosen as best, the number of times it is chosen as worst, and then subtracts them. Here you can see that type of provider is ranked first, travel time as second, and cost as third, and then so on. This result can also be obtained using conditional logit regression and the coefficients are interpreted as ranking implied by the ordering.

It's been noted by various authors that with best-worst scaling, Object Case 1, no conclusions regarding the relative importance of attributes measured by marginal rates of substitution are possible.

Now, on to DCEs. DCEs are the most common stated preference method applied in health to elicit and quantify preferences and trade-offs. This is a simple example of a 2-alternative, forced-choice DCE. This DCE example has 3 attributes, a benefit attribute, a risk attribute, and a process attribute.

Profiles are constructed from attributes with varying levels. The profiles are then combined into choice tasks, and each choice task has a different set of profiles that's determined by an experimental design. The respondent is asked to choose one alternative in each choice task, and in this example, alternative 1 is preferred to alternative 2. Each respondent then completes a series of choice tasks that are based on the experimental design, and in this situation 3 choice

tasks are displayed here.

Two common types of opt-out formats in DCEs are shown here, on the left what's called a single-response opt-out or status quo, and on the right is a dual response format where the forced-choice task is step 1, and then it's followed by an opt-out alternative choice task in step 2.

Given that decisions in real life include the ability to opt-out, it's important that DCE choice tasks reflect these possibilities. Not allowing opt-out may result in biased estimates and overestimates of preferences and utilities.

The decision to include an opt-out depends on the research objective. When the objective is to determine the expected participation in a program, such as cancer screening, it's recommended that an opt-out be included to reflect the actual choices of the target population. Using a dual response format reduces the loss of information in situations where a large proportion of the sample of respondents might choose opt-out.

What do DCEs measure? This is a generalized and stylized representation of the indirect utility function, which includes the attribute levels plus a random error term. The pattern of choices provides data for regression analysis to estimate coefficients or beta parameters that provide relative preference weights for each attribute level. The difference in preference weights then reveals the impact of a change in attribute levels on utility.

We can estimate a variety of measures from these data with of course the caveat that these are relative measures in the context of and conditional on the attribute and range of attribute levels. We can actually obtain a lot of information from DCE results, and most simply are the first two rows in this table.

We can look at the direction of preferences based on the positive or negative signs on the beta parameters. We can look at the ordering of the attributes, looking at the order of each of the attributes and the levels; and then if we move on

to other rows, we can also compare attributes in a number of other ways.

The first is the utility associated with changes in the attribute levels here; marginal rates of substitution from trade-offs between changes in attribute levels; and there's a variation of marginal rates of substitution that's the specific example of maximum acceptable risks. This is the risk equivalent of the greatest increase in risk for which a patient would accept a given benefit improvement.

This is a simple example to illustrate. Here we have a DCE with 2 attributes and 3 levels each. We can look at these findings from a conditional logit analysis of a DCE, and they're interpreted similar to any other regression.

First we can look at the direction of preferences from the beta parameters, and these seem logical. Higher effectiveness is preferred to lower and fewer side effects are preferred to more. Next, we can look at the relative importance. We can look at the marginal utility of improving

effectiveness and the marginal utility of reducing side effects from one attribute to another. This can be estimated by the associated differences in the beta parameters.

A third thing that we can look at is something we called relative attribute importance, which is shown here in the table at the top. These can be calculated by assessing the absolute difference in the attribute level beta parameters for one attribute, so effectiveness on the top here, divided by the sum of the absolute difference in attribute level beta parameters for all attributes. Although this measure is commonly reported, DCEs actually only measure choices between attribute levels and not between attributes.

We can also compare changes between attributes down here lower in the slide, and marginal rates of substitution are trade-offs between changes in attribute level. For example, how many points of effectiveness would patients be willing to give up to reduce side effects from

2 percent to 1 percent, and in this example, it's 3.

Then finally, a variation is the maximum acceptable risk, and the MAR can be estimated as the utility increase for a given benefit improvement divided by the utility increase for a 1 percent risk increase. Here in this example, patients would on average be willing to accept a 1.3 percent increase in side effects for improving effectiveness from 6 to 10, which is a package of 4 points of benefits.

So we covered a lot in a short time, and this slide compares BWS and DCE in terms of analysis and interpretation. I would like to highlight that BWS is focused on attributes only. In contrast, DCEs include attribute levels. With DCEs, trade-offs can be assessed as marginal rates of substitution and estimates of maximum acceptable risk.

There are a variety of analytical approaches that can be applied down here in the bottom of this slide. For BWS, some use something called the log

square root ratio statistic or normalized count different scores. There are different ways to analyze these data.

Then I'd also like to point out that although conditional logit is the basic analysis, extensions such as random parameter logit are appropriate. These account for correlations between repeated measures, then we also use things like latent class analysis to look at preference heterogeneity.

Now to finish, a few words on good research practices for preference-based methods. Preference studies need to be valid, relevant, and feasible. These are the 11 recommended qualities used by the FDA when deciding whether PPI constitutes valid scientific evidence, and I've grouped them into these four different categories. As requested by the FDA, I will highlight only those in red for this session today.

Quality number 3 suggests that we follow guidelines for good research practices that are established by recognized professional

organizations such as the International Society for Pharmacoeconomics and Outcomes Research.

ISPOR has published three widely recognized and cited task force reports on preference methods. The first provided broad guidance, the second focused on experimental design, and the third on analysis. There's also a fourth task force in progress that is shifting from the methods aspects to using patient preferences to inform decision making.

This is a figure on this slide reflecting the checklist from the first ISPOR task force. This provides a really nice structure of the steps in developing, designing, analyzing, and reporting preference studies.

Preference studies require a clear objective and a research question supported by qualitative research and testing. This requires early consultation with decision-makers and patients to identify whether or not a decision is preference sensitive and the context in which the preference information will be applied.

BWS and DCE are in that [inaudible – audio gap] survey, and preferences are only one component of that survey. Typically, the survey also includes background questions, descriptions of the attributes and levels, tests of validity and reliability, and demographic questions. I'd also like to say pre-testing, more pre-testing, and then pilot testing and engaging patients, clinicians, and researchers in this is critical before fielding the study.

Alright. On to the next. Quality 2 is about relevance. Good research practices identify and select all important and relevant attributes and attribute levels, and the first step is to identify potential attributes to describe the alternative.

In addition to reviewing the literature, qualitative methods such as interviews and focus groups are used to identify what attributes are important to patients and determine the number of relevant attributes. It is important not to omit any relevant attributes. Qualitative research also

helps us understand the way in which people describe the attribute.

The second step is to select the attributes and levels, and that's often challenging because the number of possible attributes identified typically exceeds the number of attributes that are feasible to include in your study. In selecting those attributes, researchers need to strike the balance between what's important to patients, what's relevant to the research questions, and what is relevant to the decision-making environment. Levels should encompass the full range of salient values, not necessarily all possible values, and they can be categorical, continuous, or probabilities.

Quality number 4 is about the study population, and it states the study should measure preferences of a representative sample of adequate size so that the study results can be reasonably generalized to the population of interest. Of course, this is a function of both the sample size and the sampling frame for your study. Larger

samples are typically more generalizable, but they're not necessarily relevant for specific subgroups of interest. Thus, it's important to assess the population in the context of the research question.

In general, a broader study population is more relevant for resource allocation decisions, but if you want to inform specific risk-benefit trade-offs in a high-risk subgroup -- examples would be in rare disease -- a more narrow sample of the eligible study population might be relevant.

Quality number 6 is about minimizing bias and effectively communicating benefits and risks. Both BWS and DCEs use an experimental design, and this gives researchers the control over the stimuli that's used to generate preference data and can reduce confounding and correlations.

The principles of experimental design are to obtain as much statistical information as possible to get unbiased and precise parameter estimates, so our first priority is to identify. To identify particular effects of interest, the experimental

design must sufficiently vary the relevant attribute level within and across choice questions. And in the case of higher order effects, you need to include sufficient numbers of attribute-level combinations.

The second point here is around efficiency. Statistical efficiency considers the precision of the estimate, so minimizing confidence intervals around the parameter estimates, and that needs to be balanced with response efficiency. A statistically efficient design that's too difficult or too long for patients may increase measurement error and reduce response efficiency due to high cognitive burden. Good practices suggest between 8 and 16 choice tasks are reasonable numbers in health, all depending on the complexity of the design.

Finally, communicating quantitative health information is challenging. Given varying levels of the ability to understand and use numbers, it's important to find and describe levels, benefits, risks, and uncertainty. Using appropriate methods

reflect numbers and probabilities that help patients conceptualize and process these outcomes.

This is an example of how benefits and risks can be represented in choice tasks, and good practice includes key aspects to clearly communicate the numerical values. This is by visually reflecting part-to-whole relationships using graphical techniques such as icon arrays, and then complementing this by words and the corresponding numbers.

In conclusion, designing patient preference studies are different than your everyday survey. I just wanted to highlight a couple of things from this slide. Very importantly, PPIs can be considered valid scientific evidence if a high-quality study that's relevant, valid, and feasible had been conducted. This is just like any other.

I'd also like to emphasize the importance of consulting with stakeholders in designing the preference study and conducting the qualitative research as a fundamental part of good study

design, and then followed by pre-testing, more pre-testing, and pilot testing. Then we have to bear in mind, different PPI methods capture different types of preferences, and they need to be interpreted in the context of the preference study design.

That is all for this very brief overview, and I thank you, and look forward to the discussion.

Clarifying Questions

DR. SUAREZ-ALMAZOR: Thank you, Dr. Marshall.

We will now take clarifying questions for Dr. Marshall. Please use the raised-hand icon to indicate that you have a question, and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible.

Finally, it would be helpful to acknowledge

the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Thank you, Dr. Marshall. I would like to start by asking you a question about the validity and reliability of these methods to assess patient's preferences across populations; for instance, young versus old, ethnic background or level of literacy. You touched briefly on the need for a clear understanding, so I was wondering if you could comment on this aspect.

DR. D. MARSHALL: Thank you for that question. Yes. As I commented, there are two aspects I think that are important to identify here or to reference. One is the study population to be surveyed, and two is how to communicate those risks and also the benefits.

You raise an important aspect, and that is numeracy varies in different populations, and cognition, of course, varies in different populations depending on ages. As I said in my

slide on the population objective, you want to focus primarily on the target population of interest, and in order to do that, you have to be able to use and communicate information very clearly. I would say that you have to test in the populations that you would like to survey.

If you're interested in different ethnic populations and you want to make sure you have representativeness, for example, I would make sure that you test the survey and the display of the choice tasks within those populations, and ensure comprehension

One of the things that you can do in your pre-testing -- that's why I emphasized pre-testing -- is to actually do what we call talk-aloud studies to ensure that people are understanding what it is you're asking and that they're also able to read and interpret what is it that is being displayed in the actual choice task.

So it's really useful to specifically target each of those populations where you think there may be different levels of understanding or

comprehension when you're actually doing your pre-testing of your survey.

DR. SUAREZ-ALMAZOR: Thank you.

Mr. O'Brien?

MR. O'BRIEN: Yes. Thank you, and thank you, Dr. Marshall. It's great to see PPI and try to see this as a great instrument going forward with the patients that we deal with.

I did have a question regarding good research practice and potential patient bias built into what we're looking at for the targeted populations and what your thoughts were in terms of self-reporting and online surveys.

In self-reporting in the world of scoliosis, a child is supposed to wear a brace for 21 hours on average. They will self-report 18, but in fact when you put a compliance tester in a monitor on the brace, it's really 12 hours, so you're not getting exactly the targeted population we get.

So I was just curious in terms of PPI and selecting target populations, what your thought about that was.

DR. D. MARSHALL: Yes. That's a really good question. I guess there are two levels. One is around self-report in general. As you well know, there are questions or one would always want to think about the reliability of self-report data regardless of whether it's PPI or any other kind of data.

Having said that, we are talking about patient-reported information, and therefore the patient is the source of the information. So that becomes the estimates that are relevant to use. I think it's important to be aware and do whatever testing is possible to check the validity of that.

There are also special challenges in eliciting preferences from young people, particularly children, and sometimes in survey technique proxies can be used. That is a methodology and approach that is currently under investigation, which there is a lot of research currently being done.

I would mention, actually in fact, that there are various task force reports that are being

considered because this is a really important area of research that isn't entirely defined or clear at this moment.

MR. O'BRIEN: And the validity of online surveys?

DR. D. MARSHALL: Oh, yes, thank you; the second part.

Some years ago, when we first started doing patient preference elicitations in health, there were quite a number of concerns that were raised about collecting data online and by Web I would say that in more recent years this is much less of a concern.

The reason why it was raised as a concern is about the bias, the potential bias of the respondent population being typically of a higher socioeconomic status and also being more literate or being able to access those technologies and use those technologies.

I would argue today that those concerns are much reduced because a very large proportion of the population now has access to these technologies and

are very well versed in being able to use the internet or online types of technology. Unfortunately, I guess in the current situation of our pandemic, I think even more people are becoming very literate in using online tools, and this would cut across all age groups actually. So I think those concerns about online reliability or validity are much reduced.

MR. O'BRIEN: Okay. Thank you very much.

DR. SUAREZ-ALMAZOR: Dr. Hovinga?

DR. HOVINGA: Thank you. I'm Collin Hovinga. Thank you for your presentation, Dr. Marshall. I really enjoyed it and really admire your thoughts. I had a question about sample size and determining what is an adequate sample size to consider at least what's representative or what is statistically valid in a methodology in this type of research.

Could you comment to that as we think through that space? Thank you.

DR. D. MARSHALL: Yes. This is a great question. Sample size is not something I had the

time to go into, but it is obviously relevant. There have been studies done and published in the literature around PPIs looking at what are the appropriate sample sizes. There are a few different ways to approach that. One is looking empirically and also looking at the standard errors of estimates.

What we've observed in the literature from work that's being done, and this is over many, many studies, is that between 150 and 300 is a really good sweet spot, if I could say, with respect to standard errors. So you're probably going to get reasonable estimates based on those sample sizes.

I would also say that if you're interested in subgroups within that population, each of those subgroups would ideally have that sample size. So if you want to do that subgroup analysis, you have to think about sample size for each of those.

The other thing to bear in mind with sample size is that it is going to be dependent on the complexity of the choice task and the attributes that are being included in the actual question.

The more risk attributes that you have included, I would say the more complex it gets, and it's going to increase the need for sample size. So that's also a consideration.

There are formulas to calculate sample size for choice tasks and preference-based work, but they're a little more complicated, as you can imagine, than when one is thinking about looking at a primary outcome in an effect size in a clinical trial because you're looking at multiple attributes and looking at the dynamics of all of those attributes and changes in the utility for each of the attributes levels relative to one another. So there are a lot of moving parts in terms of looking at the sample size.

DR. SUAREZ-ALMAZOR: Okay. Thank you.

Dr. Nason?

DR. NASON: Hi. Martha Nason. Thanks for that presentation. I guess just one thing I've always wondered about is it seems that any of these methodologies could be really influenced by the way, for example, risk is described, how the words

are chosen or how much space is given to that in terms of trade-offs between risk-benefit.

I was just wondering if there is any sort of wisdom on having possibly different versions written by different people or some way to assess how much the way that a question is framed and the level of detail about risk influences people's choices.

DR. D. MARSHALL: Yes. Thank you; another really good question. Framing of course is really important, and it would probably be challenging to say that there is a single best way to do this. That is actually why doing the qualitative research is so important in addition to doing pre-testing to discuss with your potential respondent groups the extent to which they're interpreting and understanding what it is you're asking.

I guess my advice would be, yes, be very cognizant of framing effects. There are also known framing effects with respect to whether risks and benefits are framed in a positive way or a negative way because they can be presented using different

words, as you say, or different framings. The other is to be cognizant about how people are actually interpreting. So again, in pre-testing exercise, it's really important to talk to your respondents and ensure that they're able to understand what it is you're asking them.

The other thing we do is we typically build in what we call warm-up questions in our surveys to get people familiar with the tasks, and we also build in -- and this goes back to the first question that was asked in this question period. We also build in tests of reliability and validity within the actual survey in the choice-task questions.

So there's a range of different tests that can be built in to ensure that people are actually interpreting and understanding the questions correctly. All of these techniques and approaches are used to try to mitigate that, follow good research practices, and at the very least you want to make sure that you're very cognizant of how things are framed, how they're presented, and

therefore, how to interpret them. You also will want to test that in multiple populations to ensure that all participants can reasonably [inaudible].

DR. NASON: Thank you.

DR. SUAREZ-ALMAZOR: We are running a few minutes late, so we are just going to take the last question for Dr. Marshall.

Dr. Singh?

DR. SINGH: Hi. Jasvinder Singh. Thank you for the good presentation. I was wondering, Dr. Marshall, the risks can sometimes vary across different age groups or some patient characteristics such as comorbidity. Frequently, the side effects of several of our medications or competitor medications may go up by age. I understand that trying to balance feasibility and comprehension, you can't show a variety of risk ranges by a specific characteristic.

What are the ways to get around this other than having several groups of people that go across the characteristics? Are there other scientific methodologies that can provide some insights into

what went into that thinking process when the risks might vary because we're presenting average risks in some of these? Thank you.

DR. D. MARSHALL: Yes. Preferences studies actually provide a really good opportunity to look at ranges of values. Your attribute levels need to be selected carefully in order to represent the possible range of plausible values.

So if you're talking about risk values, you would want to represent what we know, based on best knowledge to date of what the plausible risks might be, and then you might also want to extend that a little bit more as well, to squeeze the tail as they call it, in order to make sure we think about the possibility of risks that could potentially be a bit outside of the existing known range of those risks.

The reason we do that is so that we can actually make inferences around the results of our studies, and we want to make sure we capture the reasonable extremes that would represent existing and plausible alternatives of risks.

When we look at those different levels, you might have a range of risks. I think in the example I showed, it was from 1 percent to 5 percent. You would want to make sure that that does capture the relevant range of plausible risk numbers that are going to be presented to people so that you're capturing the complete range of possibilities.

DR. SUAREZ-ALMAZOR: Thank you, Dr. Marshall.

The FDA has just notified me that Dr. Marshall will not be here for the rest of the meeting. So I said these would be the last questions, but as she will not be here to respond later, does anyone else have any other questions? If so, please raise your hand; if not, we will move on.

Dr. Calis?

DR. CALIS: Yes. Thank you very much, Dr. Marshall, for a very enlightening presentation. It's sort of new to me. I don't have expertise in this particular area, but I think it's really

important, and you presented a very elegant model that allows patients to voice their preferences in a more robust and more meaningful fashion than we have in the past with other approaches, so I appreciate that.

One of the questions I want to come back to, because I think you were asked a question about this, I want to delve a little further into the patient's understanding and their perception of the risks. I can sort of appreciate how patients would -- things that they can experience, things that they can perceive themselves, they've felt in the past, et cetera, and perhaps they can truly appreciate.

But in terms of things of the nature that might be initially things that we might pick up in a more objective fashion that they might not really perceive -- radiologic changes and other types of changes that patients might not perceive -- do they really have a true understanding of that, and can they factor that into an equation where they themselves can then balance risk versus benefit?

DR. D. MARSHALL: Yes. Thank you for that, indeed. This is where it becomes really important. Remember I mentioned that in the survey, you do describe to people. You don't just present these choice tasks that I've been showing you in the presentation. There is a whole aspect of the survey where, A, we would collect information about the people in the survey to understand their experiences, their demographics, et cetera, so that we can describe who is actually in our sample. That's really important.

The other thing is that we do describe in words, in patient-friendly language, and we usually test that many times, each of the different attributes that are included in the choice tasks; and we do that in order to explain the context, what the implications are, what it means for them, and make sure that everybody who's responding has that background information upon which to reflect.

So yes, in our pre-testing, we can check if in fact they understood this background material. Then, two, when they're going through the survey

again, we can debrief afterwards -- that's often a technique that's used -- to make sure they understand it.

I guess to the extent that it's possible, I think that we try to design preferences surveys in a way that we have provided as much information and in a balanced way that's possible. Admittedly, there may be things that -- you're right -- people wouldn't necessarily feel, so we're describing that to them as a possible risk.

I guess that would be similar, though, in a clinical situation where you might be explaining the potential risks of a treatment to a patient, and they have to basically try to understand this and make those choices.

So we try to inform them as best as possible, have different strategies methodologically to try to make sure that it's balanced and that they're comprehending the question. Then at some point, yes, different people may have different perceptions of this. But people make these decisions in real life, so we're

essentially trying to collect these kinds of decisions as best as we can, with as much information communicated in as clear a way as possible.

DR. CALIS: Thank you.

DR. SUAREZ-ALMAZOR: Ms. Johnson?

MS. JOHNSON: Thank you. This is Hetlena Johnson. One quick clarifying question I have, and I think Dr. Calis was on the same path of what I was going to ask, and I may not have heard this as we were going through it.

In terms of actually debriefing the patient and making sure, and testing the sample, and their understanding of the types of questions that were asked of them, is any audio used in those types of debriefings or introducing the questions? Is anything presented via audio besides via words and understanding it, the questions that are being asked? Thank you.

DR. D. MARSHALL: Yes. That's an interesting question. There are different formats, and this actually goes back to one of the earlier

questions as well. Preference information has been used successfully with a wide range of populations, particularly in populations that may not be as literate, either innumeracy or otherwise.

We often introduce pictures, and there are multiple examples of discrete-choice experiments where the attributes are, I can say, heavily described in pictures as well as words, and sometimes without words, in order to reflect specific attributes.

We can communicate in different ways. The reason why I mentioned that is you mentioned audio. One of the things that has been introduced more recently in DCE and has been used in a [inaudible] is the idea of pairing the background material using audio, actually, where there's material presented through actually audio-visual, and the respondent would get a briefing in that way. So that's also an option that can be used to try to ensure and increase understanding of the respondent populations with respect to what's being asked.

In terms of the actual debriefing itself,

typically we would do that in person. It may be audio recorded for the purposes of taking notes. All of these things would need to be done with appropriate consent, et cetera. But I think there's a range of different approaches that people have been using in order to do debriefing. Typically, we would do that in person.

DR. SUAREZ-ALMAZOR: Thank you, Dr. Marshall. I believe there are no more questions, so we will move on.

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

For this reason, FDA encourages all participants, including Pfizer's non-employee presenters, to advise the committee of any financial relationships that they may have with the sponsor, 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 this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Pfizer's presentations.

Applicant Presentation – Kenneth Verburg

DR. VERBURG: Thank you.

Good morning. My name is Ken Verburg. I'm the medicine team leader for the tanezumab program at Pfizer. On behalf of my Pfizer and Lilly colleagues, I would like to begin by expressing our appreciation for convening the advisory committee meeting to discuss the marketing application for tanezumab, and to members of the advisory committees for their preparation and participation in [inaudible – audio gap].

Osteoarthritis is a serious health problem that substantially impairs physical function and quality of life, particularly in patients with moderate-to-severe osteoarthritis [inaudible], and additional therapeutic options are urgently needed for those patients with osteoarthritis who do not achieve pain relief or cannot tolerate currently available treatments.

Tanezumab was developed as a new approach to treat the chronic pain of osteoarthritis and offers the potential for addressing this critical unmet need. We are seeking approval of tanezumab for use in patients with osteoarthritis and in whom other analgesic medications are unsatisfactory due to inadequate pain relief, intolerability, or a contraindication for the therapy.

Tanezumab provides clinically meaningful improvement in pain function in this target population. Tanezumab lacks the risk characteristic of NSAIDs and opioids due to a mechanism of action that is distinct from either of these medication classes. Thus, in keeping with

our target population, tanezumab may also be a benefit in patients in whom NSAIDs or opioids are not appropriate.

To summarize, tanezumab is not intended for all patients with osteoarthritis pain nor as a replacement for NSAIDs. Given societal risk and the well-being of patients, however, we want to avoid putting patients on opioids whenever possible.

Tanezumab is associated with one serious risk, rapidly progressive osteoarthritis that may necessitate a total joint replacement. We conclude the risk of joint safety events with tanezumab is outweighed by the risk of NSAIDs and opioids and is acceptable in the context of the unmet medical need of the target population and the benefits of tanezumab therapy.

Rapidly progressive or destructive osteoarthritis is not unique to tanezumab or nerve growth factor inhibitors in general. Published studies describing idiopathic rapidly progressive osteoarthritis date back more than 50 years.

Beginning at about the same time frame, parallel investigations identified analgesic hip with NSAIDs in which the reported radiologic and clinical profile was reminiscent of idiopathic rapidly progressive osteoarthritis.

Our program established that analgesic arthropathy manifested as iatrogenic rapidly progressive osteoarthritis is a risk for both tanezumab and NSAIDs, but more so for tanezumab. This view is based on 50,000 radiographs collected in 3,000 tanezumab-treated patients, advanced structural disease, and an additional thousand patients treated with NSAIDs for up to 56 weeks and 24 weeks of additional post-treatment follow-up.

The interesting point here is that two very different mechanisms to treat pain can lead to the same adverse joint outcome and suggest that altered biomechanics linked to reduced joint pain, increased joint loading, could be the common precipitating factors in combination with other joint-specific factors such as the presence of osteoarthritis or subchondral bone integrity.

Recent studies have also reported an association of accelerated joint damage in osteoarthritic knees following intra-articular corticosteroid injections.

As shown on this time line, clinical evaluation of tanezumab in osteoarthritis began in 2004. The program culminated with the commission of a marketing application in 2019. There were two successive partial clinical holds placed on tanezumab and all anti-NGF development programs over the period of 2010 to 2015, and the circumstances and the resolution of these partial clinical holds are described in our briefing document.

For all intents and purposes, these partial clinical holds separated the clinical development of tanezumab for chronic osteoarthritis pain into two phases, the pre-2015 program and a post-2015 program.

In the pre-2015 phase, a total of 17 clinical studies were conducted investigating primarily intravenous administration. When the

phase 3 clinical development program was reinitiated in 2015, three additional studies were completed. These latter studies were designed to evaluate subcutaneous administration at doses of 2.5 or 5 milligrams administered to patients for whom the use of other analgesics were ineffective or not appropriate.

Our agenda today is comprised of presentations that describe and contextualize the results of the osteoarthritis clinical development program, which two of these presentations were prepared by members of our external delegation, and I would like to acknowledge Dr. Schnitzer and Dr. Kivitz for their preparation and contribution.

The objectives of our presentations are twofold. Our first objective is to demonstrate that the benefit-risk balance of tanezumab 2.5 milligrams is positive in the context of the unmet medical need of patients with osteoarthritis, the efficacy and safety profile of tanezumab, the patient population intended for tanezumab treatment, and the proposed risk management plan.

Our second objective is to establish that the weight of evidence supports approval of tanezumab at a dose of 2.5 milligrams within the current therapeutic context of managing patients with osteoarthritis.

Well, this is my last introductory slide, and I will now turn the presentation over to Dr. Tom Schnitzer.

Applicant Presentation – Thomas Schnitzer

DR. SCHNITZER: Thank you, Dr. Verburg, and good morning. My name is Thomas Schnitzer, and I'm a rheumatologist and professor at Northwestern University Feinberg School of Medicine. While I've been compensated by the sponsor to be here today, I have no financial interest in the outcome of this meeting. My goal this morning is to provide an overview of the impact of osteoarthritis, its current management, and the basis for the need for better medical treatments.

Osteoarthritis, or OA, is the most common form of arthritis. It's characterized by joint pain, activity limitation, physical disability,

reduced health-related quality of life, and excess mortality. It's estimated that over 32 million Americans suffer from osteoarthritis or approximately 1 in 7 adults in this country. And as shown on the figure on the right, the prevalence is expected to continue to rise steadily over the next 20 years.

Forty-three percent of those over the age of 65 years suffer from osteoarthritis, however, what is less well recognized is that almost half of all the people with OA are of working age. Osteoarthritis used to be considered a degenerative passive disease of cartilage, but we now know it's a biomechanically mediated active process involving all the tissues of the joint, not only cartilage, but bone, meniscus, synovium, and muscle.

Pain is the most prominent clinical presentation of osteoarthritis as reported as moderate or severe in 25 to 50 percent of all osteoarthritis patients, and this is despite being on treatment.

The population suffering from osteoarthritis

has a high level of comorbidities with one-third having 5 or more chronic conditions. Plus, limitations of physical function are not surprising with 80 percent of people with osteoarthritis estimated by the WHO to have some limitation of movement and 25 percent who cannot perform their major activities of daily living.

Hip and knee OA is the 11th highest contributor to global disability, and in addition to a significant impact on quality of life, there's also been a reported increase in all-cause mortality in people with osteoarthritis compared to matched controls without osteoarthritis.

Finally, OA is costly both to society, but more importantly to individuals. Osteoarthritis is the second most costly health condition treated in the U.S. hospitals, responsible for 10 percent of all hospital admissions, over 23 million healthcare visits, and over $100 billion in OA attributable healthcare costs to society.

At the level of the individual, OA attributable earnings losses are estimated over

$4,000 a year, a significant percentage of one's annual income. Thus, the functional limitations driven by the pain of osteoarthritis are costly and markedly reduce quality of life. Clearly, based on what I've presented, our current approach to osteoarthritis treatment is not working.

On the left of this slide is an abbreviated template of the consensus among professional societies for the management of osteoarthritis. This first column of data from a combined Medicare and commercial insurance database shows the initial treatment received by patients newly diagnosed with self-reported, moderate-to-severe osteoarthritis pain. We see that opioids, considered the treatments of last resort, are actually the most common current initial therapy started in over half the patients. This finding has been replicated in many other studies.

I was required to establish the osteoarthritis data shown here from the 2019 National Health and Wellness Survey focused on people, again, self-reporting, moderate-to-severe

osteoarthritis pain, and indicate, again, more people are taking opioids than NSAIDs.

Despite the use of these medications, data from a number of prospective longitudinal studies of people with osteoarthritis, shown on the right, including the European study of osteoarthritis real-world therapies, or SORT, and the Osteoarthritis Initiative, a U.S. study of almost 5,000 people with osteoarthritis followed for over 8 years, demonstrate that 25 to 50 percent of people still report moderate to higher levels of pain, even with treatment. Furthermore, data from the Osteoarthritis Initiative showed that people continue to experience these pain levels consistently over many years.

Many of the reasons for these five things are well known. First, NSAIDs and opioids, while effective for short-term therapy for acute pain, display less effectiveness over extended periods of time as might be required in chronic pain conditions, and this is particularly the case for opioids.

Additionally and perhaps more importantly, both of these classes of drugs are also poorly tolerated so that many people discontinue treatments due not only to lack of efficacy but also because of bothersome side effects, highlighted in the my bottom figures, demonstrating on the left the percentage of people remaining under initial NSAID over time, and in a similar study on the right, reporting that more than 90 percent of patients discontinue treatment with either NSAIDs or opioids within a year, and often switch to another class of medication.

Additionally and importantly, many people are not started on these drugs or are afraid to take them due to well-known side effects. Among these side effects, for NSAIDs there are boxed warnings in the prescribing information stating that people taking NSAIDs may be at risk for fatal cardiovascular and fatal GI events. But even more importantly, in my opinion, is the fact that many people with osteoarthritis cannot or should not be taking NSAIDs due to coexisting conditions.

Over 10 percent of the osteoarthritis population may have either congestive heart failure or renal insufficiency to a degree that NSAID use would be a danger. It's been well documented that NSAID use exacerbates existing congestive heart failure and leads to increased hospitalizations. Similarly, NSAIDs increase the risk for acute kidney injury, and for people on anticoagulants, taking an inhibitor of platelet function such as an NSAID makes major bleeding significantly more likely.

Opioids, particularly in the elderly, are extremely poorly tolerated as shown by the data and table on this slide. In addition to being poorly tolerated, there's a larger concern of dependence, addiction, and abuse, conditions more likely when opioids are used longer term for the treatment of pain. These issues have led all the professional societies dealing with osteoarthritis to consider opioids drugs a last resort to be taken only short-term or not at all.

All the information I've shown you regarding

NSAIDs and opioids in chronic pain have been known for some time and spurs the quest for new treatment options. Fortunately, the advances in neuroscience the last part of the 20th century and the recognition of genetic disorders associated with abnormalities and pain sensation have provided a host of new potential targets for the pharmaceutical industry.

One, nerve growth factor, NGF, has evolved to being the focus of the discussion today. Based on promising preclinical data, a small Bay Area biotech company initiated clinical trials over 15 years ago with an antibody to NGF, what we now know as tanezumab. The rest of the story over the ensuing years is detailed in your briefing document and you will hear presented by Drs. Verburg and West.

In summary, let me reiterate, osteoarthritis is a serious disease that has a major impact on an individual's health and well-being. Treatments, while modest in efficacy, have serious liabilities that may be life-threatening. And perhaps more

importantly, many people with osteoarthritis cannot or should not be taking these drugs due to comorbidities or issues of tolerance. We definitely need additional effective and safe drugs for these individuals.

Thank you very much for your attention. I'll now turn the presentation over to Dr. Verburg.

Applicant Presentation – Kenneth Verburg

DR. VERBURG: Thank you, Dr. Schnitzer.

Over the next 15 minutes, my intention is to review the efficacy profile of tanezumab, drawing upon studies completed both during the pre-2015 and post-2015 periods as outlined on this slide. My primary focus will be the post-2015 studies.

While this slide summarizes the key aspects of the efficacy profile of tanezumab in patients with moderate-to-severe osteoarthritis, tanezumab 2.5 milligrams, administered subcutaneously every 8 weeks, provides consistent and clinically important improvement in pain and function.

The efficacy of this dose is established in

patients for whom the use of other analgesics are ineffective or not appropriate and is similar across demographics, disease severity, and geographic subgroups. There are no meaningful efficacy differences between tanezumab 2.5 and 5 milligrams. Finally, the efficacy of tanezumab 2.5 milligrams is durable over long-term treatment.

The pre-2015 studies were conducted with intravenous administration of tanezumab. Typical tanezumab plasma concentration profiles, comparing intravenous and subcutaneous administration of tanezumab 2.5 milligrams, are nearly superimposable, beginning approximately 4 weeks after treatment initiation for the remainder of the 8-week dosing interval.

As a result, the efficacy outcomes with intravenous administration provide relevant and important evidence to support the results observed with subcutaneous tanezumab administration. These profiles were determined from a population pharmacokinetic model of over 4400 patients and more than 18,000 concentration measurements.

Two placebo-controlled osteoarthritis studies completed during the pre-2015 period are summarized on this slide. Both studies evaluated tanezumab at doses of 2.5, 5, or 10 milligrams administered by intravenous injection at 8-week intervals.

Eligible patients for the studies were required to have moderate-to-severe knee or hip osteoarthritis and an unsatisfactory experience with non-opioid medications such as NSAIDs, or were a candidate for a total joint replacement or another invasive intervention.

All tanezumab doses in both studies were superior to placebo treatment. This table summarizes the co-primary efficacy results by study and tanezumab dose levels within each study as shown in the far-left column. Each check mark indicates tanezumab provided a statistically significant improvement versus placebo treatment at the week 16 landmark analysis.

The WOMAC pain results at week 6 are shown in the graph in the right panel. Patients recorded

their pain level using an 11-point numerical rating scale with zero representing no pain and 10 representing extreme pain.

Mean baseline scores in tanezumab-treated patients improved substantially, decreasing from severe pain levels at baseline to mild pain during treatment. The magnitude of efficacy with tanezumab 2.5 milligrams was similar to the higher doses of tanezumab in Study 1011 and marginally lower in Study 1014.

Patients completing Studies 1011 and 1014, or two other pre-2015 phase 3 osteoarthritis studies, were permitted to participate in Study 1016, which was a long-term, open-label, dose-blinded extension study.

The mean improvements in pain from baseline depicted on this slide are from the cohort of patients who were treated continuously with tanezumab beginning in the parent study and then continuing throughout the course of Study 1016. Each dose of tanezumab provided durable efficacy over 48 weeks of treatment with minimal improvement

in efficacy observed with escalating doses of tanezumab.

My next topic is the post-2015 osteoarthritis studies. We completed two placebo-controlled studies during this time frame. The first of these was Study 1056, which was conducted in patients with moderate-to-severe knee or hip osteoarthritis.

Tanezumab 2.5 milligrams was one of the active treatment arms in the study. In the second active treatment arm, all patients received tanezumab 2.5 milligrams for their first administration of study medication, and then tanezumab 5 milligrams for their second administration. Primary assessment of efficacy was at week 16, and following the treatment phase, patients were followed for an additional 24 weeks to monitor for safety.

The design of the second placebo-controlled study, Study 1057, was similar to Study 1056 with the following exceptions. First, the duration of treatment was extended to 24 weeks with patients

receiving 3 subcutaneous administrations of study medication; and second, tanezumab 2.5 milligrams and 5 milligrams alone were evaluated as parallel treatment groups over the course of the entire 24-week treatment period.

A brief summary of the patient demographics pooled across these two post-2015 placebo-controlled osteoarthritis studies is shown here. Patient demography was broadly consistent with the overall population of patients diagnosed with osteoarthritis.

Patients who participated in these studies had moderate-to-severe symptoms associated with their osteoarthritis at baseline as evidenced by mean WOMAC pain and physical function scores of 7 and a patient's global assessment score of 3.5 or midway between fair and poor. Approximately one-quarter of the patients were classified with severe osteoarthritis at baseline.

Patients enrolled into either of the studies exhibited advanced structural osteoarthritis disease severity at baseline. As designated by the

arrows, greater than 75 percent of patients were identified with Kellgren-Lawrence grade 3 or 4 severity of their index joint and had multiple joints impacted by osteoarthritis.

Patients participating in either of the post-2015 placebo-controlled studies were required to have a documented history of an unsatisfactory outcome -- acetaminophen, NSAIDs and opioids, or tramadol -- or be unwilling to take opioids.

The percentage of patients who met the inclusion criteria for an unsatisfactory outcome with oral analgesic medications prior to the study entry are displayed as stacked bars on this slide. As shown, all patients in both studies reported inadequate pain relief with acetaminophen as was required by protocol. Approximately 90 percent of patients in both studies reported inadequate pain relief with NSAIDs, while the remaining 10 percent cited reasons related to intolerability or a contraindication.

The use of opioids or tramadol across the two studies differed, reflecting geographical

differences in the prescribing patterns across the regions where the two studies were conducted. However, in either study, the most common reason for discontinuation or non-use of opioids was unwillingness to take these medications; and for tramadol, the most common reason provided was for inadequate pain relief.

Approximately 10 percent of patients receiving tanezumab in Studies 1056 and 1057 withdrew before completing their full course of treatment as compared to 15 to 17 percent of placebo-treated patients. The incidence of withdrawal due to treatment failure was lower for tanezumab-treated patients compared to those receiving placebo in both studies. The incidence of withdrawal due to an adverse event were low across the treatment groups, and no treatment differences were evident.

Both dose regimens of tanezumab provided consistent and significant symptomatic improvement over placebo treatment across the pain, function, and global co-primary efficacy measures at week 16,

Study 1056, and there were no marked differences between the tanezumab dose regimens in the study.

A similar profile was observed in Study 1057. Tanezumab provided a significant improvement versus placebo treatment across the three co-primary efficacy measures at the week 24 landmark analysis, apart from the patient global assessment, 5 milligrams; and there were no marked differences between the dose regimens in this study that were found.

Tanezumab provided sustained efficacy within consecutive 8-week dosing intervals. Both tanezumab doses were associated with significant pain efficacy compared to placebo at the very first clinic assessment; that is 2 weeks after their initial dose, which was maintained throughout this dose interval, as well as the subsequent 8-week dose intervals.

Tanezumab provides clinically important improvement in osteoarthritis pain. The categorical results of the WOMAC pain subscale for Studies 1056 and 1057, at week 16 and 24,

respectively, are shown here. Based on published studies, a 30 percent or greater improvement is considered clinically meaningful or moderately important, while a 50 percent or greater improvement is considered to be a substantial improvement.

A greater proportion of patients reported 30 percent or greater or 50 percent or greater improvement in pain with tanezumab 2.5 and 5 milligrams in both studies. The results with tanezumab 2.5 milligrams were again similar to 5 milligrams for either outcome.

Clinically important improvement of pain was also investigated by analyses of continuous or sustained improvements in WOMAC pain defined as a 50 percent or greater improvement from baseline or absolute pain scores of 0 to 3 representing mild to no pain.

Over weeks 4 through 16 in Study 1056 and over weeks 4 through 24 in Study 1057, both doses of tanezumab were associated with a significantly greater percentage of patients with sustained

meaningful improvement in pain over placebo treatment.

Study 1058 was the third osteoarthritis study that we conducted during the post-2015 time frame. This study was designed first and foremost to evaluate the joint safety profile of tanezumab over 56 weeks of treatment and an additional 24 weeks of post-treatment follow-up. To perform this long-term assessment, we included an NSAID treatment arm as the control group for the study, as a placebo treatment group was considered neither feasible, nor ethical.

Patients eligible to participate in Study 1058 were required to have been tolerating NSAID treatment and receiving benefit from the therapy to participate in this study. On average, patients had been taking NSAIDs for a period of 4 years prior to study entry. Patients were also required to have a documented history of an unsatisfactory outcome with acetaminophen, opioids, or tramadol.

Patients reporting moderate-to-severe pain,

physical function, and a global score of fair or worse at baseline were randomized to 1 of 3 treatment groups: tanezumab 2.5 milligrams, 5 milligrams, or an oral NSAID comprised of naproxen, celecoxib, or extended-release diclofenac at maximally-labeled doses. Efficacy was assessed over the entire 56-week treatment period, however, week 16 was the prespecified primary or landmark efficacy time point.

Demographics for the patients enrolled into Study 1058 are summarized here. Patients participating in the study were a few years younger in age and a greater proportion were black or Asian [inaudible – audio gap]. Patients enrolled into the study had moderate-to-severe symptoms at baseline, associated with their knee or hip osteoarthritis. The mean baseline pain functional and global scores were comparable to the post-2015 studies.

Patients enrolled into Study 1058 also had advanced structural osteoarthritis disease severity at baseline. As designated by the blue arrows,

approximately 70 percent of patients had a Kellgren-Lawrence grade 3 or 4 severity of their index joint and multiple joints impacted by osteoarthritis.

The overall proportion of patients who discontinued tanezumab treatment was approximately 55 to 60 percent over the 56-week treatment period. Approximately 20 percent of these patients discontinued treatment after failing to meet the protocol-mandated efficacy criteria at week 16.

The incidence of withdrawals due to treatment failure was significantly lower, though, for patients treated with tanezumab as compared to those treated with NSAIDs, and the incidence of adverse events leading to withdrawal was highest with tanezumab 5 milligrams.

The results across the three co-primary measures of efficacy at the week-16 landmark analysis are shown on this slide. Little difference among the treatment groups was observed; although in the case of tanezumab 5 milligrams, small improvements in WOMAC pain and physical

function reached statistical significance versus NSAIDs.

So, how do the results of Study 1058 contribute to our understanding of the efficacy? The range of possible week-16 efficacy outcomes from Study 1058 at the onset of the trial included superiority or comparability, and over long-term treatment, durable waning or lack of durable efficacy. The study did not include a prespecified assessment of noninferiority.

The study results with tanezumab 2.5 milligrams were consistent with clinical comparability to NSAIDs at week 16 with durable efficacy throughout one year of treatment. There are two possible interpretations of this outcome. The placebo component to the active treatment efficacy responses may have been larger than anticipated and blunted the assay sensitivity of the study, or the efficacy of tanezumab 2.5 milligrams may not be greater than NSAIDs in patients who are tolerating NSAID therapy and receiving at least a benefit.

Nonetheless, tanezumab 2.5 milligrams does not have to be superior to NSAIDs to be efficacious in a target population. Given the differences in the mechanism of action, tanezumab 2.5 milligrams would still offer the potential for benefit in patients who had an inadequate response or were unable to take NSAIDs as was shown in Studies 1056 and 1057.

In conclusion, in the treatment of chronic pain associated with osteoarthritis in patients for whom the use of other analgesics is ineffective or not appropriate, tanezumab 2.5 and 5 milligrams administered by subcutaneous injection every 8 weeks provide consistent and clinically important improvement in pain and physical function in knee or hip osteoarthritis.

Tanezumab 2.5 milligrams is a fully efficacious dose. No meaningful improvements in the onset, magnitude, or duration of analgesia are evident with escalating doses, and the efficacy of tanezumab 2.5 milligrams is maintained over long-term treatment.

I will now turn the presentation over to Dr. Christine West.

Applicant Presentation – Christine West

DR. WEST: Thank you, Verburg.

In the next segment of our presentation, I will present the safety profile of tanezumab for the treatment of osteoarthritis. The safety profile of tanezumab is well characterized, so my presentation will focus on safety topics where we noted differences relative to comparator treatments. It will include a high-level overview of tanezumab's general safety profile and key peripheral neurological safety data, and then I will conclude with a detailed review of the joint safety data.

This slide summarizes the key components of the safety profile for tanezumab 2.5 milligrams administered subcutaneously in patients with osteoarthritis. The overall adverse event profile was not notably different from that observed from the placebo and NSAID group.

The safety profile of tanezumab was

generally consistent with a dose-dependent increase in adverse events related to musculoskeletal and nervous systems when compared to placebo or NSAID treatment. Based on rigorous assessments of sympathetic nervous system safety, tanezumab was not associated with an increased risk for sympathetic autonomic neuropathy.

The safety profile of tanezumab does not suggest an increased risk for adverse events in other organ systems, including the cardiovascular system, nor in association with potential drug abuse, dependence, or withdrawal. Evaluation of a variety of subgroup analyses indicated the adverse event profile in the subgroups and the overall patient population were similar. Lastly, tanezumab was not associated with any clinically meaningful changes in laboratory values, vital signs, or ECGs.

After evaluating the clinical and safety databases, we identified the adverse events summarized in this table as those likely associated with tanezumab 2.5-milligram treatment. The associated events are either related to the nervous

system or musculoskeletal and connective tissue disorders. Both areas I will discuss further in subsequent slides. The third event type associated with tanezumab 2.5 milligrams was peripheral edema.

These events were typically mild to moderate in severity and rarely led to discontinuation. In addition, no notable relationship between the incidence of peripheral edema and hypertension, congestive heart failure, or other abnormalities was identified.

Due to the role of nerve growth factor and the mechanism of tanezumab, we have been focused on the assessment of peripheral neurological safety throughout the tanezumab clinical development program. I will now review key data from our neurological assessment.

In all clinical studies, we analyzed adverse events related to abnormal peripheral sensation, which are shown in this graph for placebo-controlled osteoarthritis studies. The overall incidence is shown on the left, followed by the most common individual adverse events moving across

the figure.

The profile for these adverse events generally shows a dose-responsive increase for tanezumab. A large majority of events were mild or moderate in severity, and they resolved by the end of the study.

Parasthesia and hypoesthesia were the most common adverse events of abnormal peripheral sensation. Patients who had an adverse event of abnormal peripheral sensation were referred for a neurological consultation. The graph on the right provides a summary of the diagnoses for these events as determined by an external consulting neurologist. For this graph, I'm going to focus on the data outlined in green.

Mononeuropathy and radiculopathy occurred in approximately 1 percent of tanezumab-treated patients and were more frequent compared to the placebo-treated patients. Carpal tunnel syndrome was the most common type of mononeuropathy.

In contrast, the incidence of polyneuropathy was low at approximately 0.2 percent and similar

between the tanezumab and placebo groups. This is important because neurotoxic agents and diseases that injure peripheral nerves typically demonstrate symmetric polyneuropathic changes, neither of which was associated with tanezumab treatment.

Lastly, I'd like to draw your attention to the blue box on the bottom of the slide, which provides a summary from intraepidermal nerve fiber density studies in which there was no evidence of a reduction in nerve fiber density, indicating tanezumab did not impact the viability of these neurons. Overall, our comprehensive evaluation of the peripheral neurological data indicates tanezumab does not increase the risk of peripheral neuropathy.

I will now move to a detailed discussion of the joint safety profile of tanezumab. As an introduction to the joint safety section of my presentation, I will spend a few minutes discussing some of the key structural changes associated with osteoarthritis and how they relate to rapidly progressive osteoarthritis.

New insights into the pathogenesis of osteoarthritis have shown it is a heterogeneous disease of the whole joint. Structural changes involving cartilage, subchondral bone, the meniscus, synovium, and periarticular muscles are associated with osteoarthritis.

The severity of osteoarthritis can be estimated by semi-quantitative radiographic scoring systems. The two most widely used systems are Kellgren-Lawrence grading, which was used in the tanezumab program, and OARSI atlas of radiographic features of osteoarthritis. The loss of articular cartilage and meniscal changes contribute to the loss of joint space risk, which is a surrogate measure of disease progression. The visual assessment of joint space width is a component of both the Kellgren-Lawrence and OARSI grading systems.

These knees images illustrate the key characteristics of the five grades of the Kellgren-Lawrence grading scale. I would like to draw your attention to the degrees of joint space

narrowing, highlighted in blue text, associated with each grade. Joints that start to show decreases in joint space width and have possible joint space narrowing are classified as grade 2, which is shown in the middle image.

More joint space narrowing is required for grade 3, as these joints have definite joint space narrowing that is clearly visibly apparent. For grade 4 joints, there is marked joint space narrowing, and this grade is often referred to as bone-on-bone, end-stage osteoarthritis. The Kellgren-Lawrence grading system also includes criteria for hip joints that are similar to those used for knees.

While the trajectory of osteoarthritis progression is not clearly understood, joint space narrowing has been noted to occur in an atypical fashion in some patients. Idiopathic, rapidly progressive osteoarthritis is an uncommon subset of osteoarthritis that has been identified in the hip, knee, and shoulder. Characteristics of the condition include severe pain, rapid loss of joint

space width visible on sequential radiographs, and severe progressive atrophic bone destruction.

Based on the available data, it is not clear if the two apparent phases of loss of joint space width and progressive bone destruction are a continuum or represent two different disease processes. Later in my presentation, I will provide the definitions of rapidly progressive osteoarthritis used in the tanezumab clinical program.

Many RPOA events are unilateral and result in arthroplasty. The prevalence of idiopathic rapidly progressive osteoarthritis is not well understood, but retrospective studies suggest it may occur in 1 to 3 percent of osteoarthritis patients. Not all rapidly progressive osteoarthritis is idiopathic, as the condition has also been associated with analgesic treatment, which I will focus on next.

Enhanced disease progression in a small subset of patients has been observed with NSAIDs, intra-articular corticosteroid injections, and

anti-NGS compounds, including tanezumab, as I will describe later in my presentation.

Several recent publications have described the structural changes in the knee and hip joints of patients who have been treated with intra-articular corticosteroids. A cohort study from the Osteoarthritis Initiative addressed the relationship of intra-articular corticosteroid injections to radiographic progression of knee osteoarthritis.

The hazard ratio for Kellgren-Lawrence grade worsening when comparing intra-articular steroid injection versus no injection was 3.0. The incidence of total joint replacement in patients receiving intra-articular corticosteroids ranged from 22 to 31 percent, which was 4 to 6 times higher than patients who did not receive intra-articular corticosteroids.

Before presenting the joint safety data, I would like to summarize the key points I will emphasize in this section of my presentation. The incidence of rapidly progressive OA type 1 was

statistically significantly greater than placebo or NSAID treatment. Both events were identified in knee joints and did not lead to a total joint replacement. The incidence of rapidly progressive OA type 2 was low and not significantly elevated relative to NSAIDs.

When evaluating the occurrence of rapidly progressive osteoarthritis over time, risk differences for rapidly progressive osteoarthritis relative to NSAIDs were generally similar. An association between joint safety endpoints and more severe structural osteoarthritis at baseline was identified, and the incidence of total joint replacement was generally higher versus NSAIDs, but the differences versus placebo treatment were not statistically significant different.

I would now like to highlight a few key findings from the pre-2015 studies before reviewing the post-2015 data. This bar graph provides the incidence rates for rapidly progressive osteoarthritis for the treatments of placebo and tanezumab monotherapy at increasing doses of 2.5,

5, and 10 milligrams, shown in blue, as well as these dose strengths of tanezumab in combination with NSAID therapy, shown in green, and an active comparator, shown in orange on the far right.

The notable findings are that there was a dose-responsive increase in rapidly progressive osteoarthritis events with tanezumab monotherapy at the dose increase from 5 to 10 milligrams, and this increase was further elevated threefold when tanezumab was administered in combination with chronic NSAIDs.

Based on this finding, the chronic use of contaminant NSAID therapy was restricted in the post-2015 studies. And as you will hear later in our presentation, we plan to also include this as a postmarketing risk minimization measure.

For the remainder of my presentation, I will focus on data from the post-2015 studies. These studies included a high degree of surveillance with scheduled imaging visits. Musculoskeletal radiologists read all images collected in these studies. Radiographs reflected in a standardized

manner at screening, as shown on the left, and in approximate 6-month intervals for longer term studies, and at the end of study visits for all studies, as shown on the right.

MRIs were collected at scheduled time points throughout the large joint safety study, 1058. Similar to clinical practice, these MRIs were read for equivocal radiographs or if the investigator requested the MRIs be read. In addition, for-cause MRIs could be collected, in red, at any time post-baseline. Across the studies, approximately 5 percent of patients had MRIs read by the central leaders to complete the safety assessment during the studies.

We designed our programs to utilize radiographs to determine eligibility of patients, so MRIs were not used for this purpose. In the three post-2015 osteoarthritis subcutaneous studies Dr. Verburg discussed in his presentation, over 13,000 patients were screened radiographically and over 4500 patients were randomized into one of the three studies.

The table on the right shows data from the patients who were radiographically screened for the osteoarthritis studies and did not qualify due to exclusionary joint conditions. These findings provide an estimate of the background rate of these conditions in the patient populations.

Severe malalignment and subchondral insufficiency fracture were the most common defined exclusionary findings in the knee, and osteonecrosis was the most common in the hip. Rapidly progressive OA type 2, shown at the bottom of the table, was less common, but it was identified in 0.4 percent of hip joints and 0.1 percent of knee joints in screened patients.

Surveillance for events occurred throughout the treatment period and for an additional 24-week post-treatment period to identify potential joint safety events. Adjudicated events came from three sources, as shown in the row of three boxes in the schematic. They included investigative reported events; events identified by the central readers assessment of imaging; and we also adjudicated all

total joint replacements regardless of whether or not there was an associated adverse event or potential joint safety finding identified with imaging.

A blinded adjudication committee reviewed available information and imaging to determine the adjudication outcome, which were utilized for the analyses of joint safety.

As highlighted in the dark blue box, a function of the central reader was to surveil the potential joint safety events based on imaging findings, although we recognize this would likely lead to a degree of false positive cases being identified since the central readers did not have access to data such as clinical data summary and consultation reports like the adjudication committee did.

Despite the different remix of the central reader and adjudication committee, adjudicated events for 77 percent of patients had exact or substantial agreement between the adjudication outcome and the central reader's assessment. In

addition, for adjudicated cases that did not have a joint safety event identified, the two groups agreed 96 percent of the time.

There were six total adjudication outcomes, and four of these outcomes were included in a primary composite joint safety endpoint that are highlighted in blue on this slide. The outcome of worsening osteoarthritis was subdivided into rapidly progressive osteoarthritis type 1 or type 2; normal progression of osteoarthritis; and not enough information to distinguish between rapidly progressive OA and normal progression.

Type 1 was based on radiographic changes and defined as a significant loss of joint space width greater than or equal to 2 millimeters within approximately one year without growth structural failure. Type 2 RPOA was defined as abnormal bone loss or destruction, including limited or total collapse of at least one subchondral surface, which is not normally present in conventional, end-stage osteoarthritis. Additional outcomes were subchondral insuffiency fractures and pathologic

fractures, both which were included in the primary composite endpoint.

The remaining two outcomes were other, which included a diagnosis and allowed the adjudication committee to specify a different outcome for events that did not meet the endpoint definition and not enough information to specify a diagnosis.

This schematic provides an overview of the adjudication outcome irrespective of treatment assignment. Across the three osteoarthritis subcutaneous studies, approximately 10 percent of patients met the requirements for adjudication. As shown in the far-left box, the most common adjudication outcome was normal progression of osteoarthritis, which consisted of events that the adjudication committee did not identify any of the primary composite endpoints, and the committee concluded the case progressed as would be expected for conventional osteoarthritis.

Normal progression of osteoarthritis was the outcome for 57 percent of patients who had an adjudicated event. Moving across the slide to the

next dark blue box, the adjudicated composite endpoint was identified in 3.2 percent of randomized patients.

Now let's look at the distribution of events by treatment group on the next slide. This graph provides a breakdown by treatment group for the 145 patients, with an event included in the primary composite endpoint on the left, as well as the individual components of the composite to the right of the dotted line.

There were no adjudicated endpoints observed in placebo-treated patients. As you can clearly see from this slide, most of these events were rapidly progressive OA type 1, as 69 percent of the total event received this classification.

For the primary composite endpoint and RPOA type 1, the treatment difference is relative to NSAIDs, for both tanezumab groups were statistically significantly different. The tanezumab 5-milligram group, shown in bright blue, had the highest event rate for the composite endpoint, as well as rapidly progressive OA type 1

and type 2, with the treatment differences versus NSAIDs for RPOA type 2 being statistically significantly different.

The event rate for RPOA type 2 in the tanezumab 2.5-milligram group, shown in dark blue, was 0.4 percent and was not statistically significantly different from NSAIDs. For both subchondral insufficiency fracture and primary osteoporosis, the event rates were similar across treatment groups.

Very few patients had more than one affected joint. For the tanezumab 2.5-milligram group, there was one patient who did, and both events were rapidly progressive OA type 1. Since rapidly progressive OA type 1 was the most common component of the composite joint safety endpoint, I'm going to focus on that outcome first in the next several slides.

These three radiographs provide an example of the progression of RPOA type 1 in the knee. The image on the left was taken at screening. The joint space width was generally maintained in the

middle image. However, in the image on the far right, taken 13 months after baseline, the medial joint space width was noticeably decreased by 2.4 millimeters, thereby meeting the definition of RPOA type 1.

Based on assessments of MRIs from patients with RPOA type 1, loss of cartilage and extrusion of the meniscus were common findings in the affected joint.

This table summarizes some key characteristics for the 101 total patients across treatment groups who had adjudicating events of RPOA type 1. There are a few points I would like to highlight. The knee was the most commonly affected joint and most events occurred in joints that were Kellgren-Lawrence grade 2 or 3 at baseline.

A majority of the RPOA type 1 events did not need total joint replacement, as 15 percent of patients with RPOA type 1 had a total joint replacement of which 4 patients were treated with tanezumab 2.5 milligrams.

We have done numerous subgroup analyses using patient and joint level characteristics to try to identify factors associated with RPOA type 1. No characteristic, other than the joint level characteristic of structural severity of the affected joint at baseline, was associated with the occurrence of RPOA type 1. I will expand upon this point further on the next slide.

We evaluated the risk differences for developing RPOA type 1 based on the baseline Kellgren-Lawrence grade of affected knee and hip joints in patients treated with tanezumab 2.5 milligrams relative to both placebo and NSAIDs. This analysis includes all joints with a given Kellgren-Lawrence grade.

On this slide, I'm presenting the risk differences relative to NSAIDs since the outcomes were similar to the placebo analyses and more patients were included in the NSAID analyses. The forest plots provide the risk differences for knee joints on the left and hip joints on the right. Within each type of joint, the subgroups of

Kellgren-Lawrence grades are shown as you move downward on each forest plot.

When considering all Kellgren-Lawrence grades of the affected joint, shown at the top of each graph, the risk difference in knee joint was 1 percent relative to NSAIDs, and for hip joints, it was 0.2 percent. When looking at the breakdown by Kellgren-Lawrence grade and joint, the risk differences within each type of joint were similar to the subgroups of Kellgren-Lawrence grades less than 4.

To provide some clinical context for the RPOA type 1 events, we compared many characteristics of the joints in patients who had RPOA type 1 or normal progression of osteoarthritis events for the tanezumab 2.5-milligram group. In general, the profiles of the two types of events were similar.

A few differences were observed. First, a higher percentage of RPOA type 1 events occurred in knee joints than for normal progression of osteoarthritis event. Next, for total joint

replacement, approximately 7-fold more normal progression of OA events resulted in total joint replacements than occurred for RPOA type 1 events. For both RPOA type 1 and normal progression of OA, a large majority of the events occurred in joints with established osteoarthritis.

When considering the clinical symptoms present at baseline for both event types in approximately 85 percent of the affected joints, the investigator identified an abnormality on the screening musculoskeletal exam, indicating they had symptoms associated with osteoarthritis. The most common findings were pain on motion, crepitus, tenderness, and decreased range of motion.

As shown in the bottom rows of data, a change in the post-baseline exam occurred more frequently in joints with RPOA type 1 than those with normal progression of osteoarthritis, although clinically significant changes, according to the investigator, were limited to approximately 15 percent of joints.

We will now take a look at the timing of the

RPOA type 1 events in the next few slides. We conducted Kaplan-Meier analyses of the data from Study 1058, which included a 56-week treatment period and a 24-week follow-up period. The differences in overall time to event in the tanezumab group were statistically significantly different relative to the NSAIDs group. The increases of events were typically identified when scheduled radiographs were taken at least 24 and 56.

After week 24, designated by the blue box on the far left, the shape of the curve for tanezumab 2.5 milligrams, shown in dark blue, and NSAIDs, shown in orange, were generally similar. This contrasts with tanezumab 5 milligrams, shown in bright blue, which had a larger increase in events at week 56, represented by the middle blue box.

To further evaluate the timing of RPOA type 1 events, we summarized the events by which interval during the 80-week observation period of the study they occurred. As shown in the left column, the overall observation period was divided

into three intervals: from baseline through the week-24 imaging visit; after the week-24 imaging visit through the week-56 imaging visit; and after the week-56 imaging visit. Both events in both treatment groups occurred in the middle interval, which was after the week 24 visit through the week 56 visit.

The forest plot on the right provides the risk differences versus NSAIDs, all of which were 1.8 percent or less. This plot lets us evaluate risk difference over time. When comparing the values for the first two intervals, the risk differences were similar, whereas the risk difference for RPOA type 1 decreased to 0.4 percent, and was the lowest for the interval after week 56 when patients were no longer being treated.

This finding suggests the risk difference for rapidly progressive OA type 1 relative to NSAIDs did not increase throughout the 80-week observation period.

As part of the patient-level risk mitigation

measures in the clinical studies, patients who had a possible joint safety event identified during the treatment period had their treatment with study medications stopped, and they were monitored for an additional 24 weeks. For the patients with follow-up imaging, no adjudicated RPOA type 1 event progressed to a more severe adjudicated endpoint like RPOA type 2 after the treatment was stopped.

Since patients with possible RPOA type 1 events did not continue to receive treatment, we do not have data regarding the possible progression of RPOA type 1 events with continued treatment. However, we were able to address the question of whether treatment of patients who had changes in joint space width at week 24, that were close to meeting the criteria for RPOA type 1, developed joint safety events by evaluating subsequent adjudicated outcomes in patients who had a joint with joint space narrowing from 1 millimeter to less than 2 millimeters at week 24 and continued to receive treatment for 48 to 56 weeks.

Across the treatment groups, 97 joints were

included in this cohort. This graph summarizes the subsequent adjudicated outcomes identified after week 24 as a percentage of joints with the specified joint space width change. For RPOA type 1, shown in the first set of bars, a lower percentage of joints in patients treated with tanezumab 2.5 milligrams subsequently developed RPOA type 1 than joints in patients treated with either tanezumab 5 milligrams or NSAIDs. No joint from either the 2.5 milligrams or NSAID groups subsequently developed RPOA type 2 after week 24.

There was one patient treated with tanezumab 2.5 milligrams who had approximately 1 millimeter of loss of joint space width in the knee at week 24, and subsequently had a total joint replacement after completing the treatment period. There was no worsening of the patient's joint space width at week 56 prior to the total joint replacement surgery, and the event was adjudicated to normal progression of osteoarthritis.

While there was not a large number of joints included in this analysis, these data suggest

continued treatment of patients with potentially important changes in joint space width did not result in increased joint safety events.

To evaluate the changes in joint space narrowing associated with RPOA type 1, an assessment of patients with RPOA type 1 in one knee also had changes in their other knee, we analyzed the change from baseline in medial joint space width in the affected knee and the contralateral knee for these patients.

As you can clearly see when comparing the profiles of the two graphs, the magnitude of changes in joint space width were larger for joints with adjudicated RPOA type 1, shown on the left, compared to the contralateral joints without RPOA type 1, shown on the right.

There were no statistically significant treatment differences between tanezumab and NSAIDs for either analysis. These findings, along with the lack of various patient-level characteristics being associated with the occurrence of RPOA type 1, support the concept that increased risk of

developing RPOA type 1 may be at the joint level rather than at the patient level.

Before presenting additional joint safety data, I would like to summarize the data findings related to RPOA type 1. The overall incidence of rapidly progressive osteoarthritis type 1 was statistically significantly different from placebo and NSAIDs, with the overall difference versus NSAIDs being 1.2 percent. Most RPOA type 1 events occurred in knee joints that had established osteoarthritis and did not lead to a total joint replacement.

When considering the timing of RPOA type 1 events, the pattern of events during the treatment period with tanezumab 2.5 milligrams was similar to NSAIDs, and the risk relative to NSAIDs decreased after treatment was stopped. Continued treatment of patients with potentially important joint space narrowing did not result in increased joint safety events. After evaluating the risk profile of RPOA type 1 events, the risk appears to be at the joint level rather than at the patient level.

I'm now going to move to a discussion of the other type of rapidly progressive osteoarthritis, which is type 2. For RPOA type 2 events across the treatment group, the affected joint was more evenly split between hip and knee joints that was observed for RPOA type 1.

Both rapidly progressive OA type 2 events occurred in joints that were Kellgren-Lawrence grade 3 or 4 at baseline, and approximately half of the patients had a total joint replacement in the affected joint. This is much higher than what was observed for joints with RPOA type 1.

The time-to-event analysis for RPOA type 2 from Study 1058 is presented on this slide. The tanezumab 5-milligram group had an earlier increase in RPOA type 2 events, and the comparison to NSAIDs was significantly different. The treatment difference between tanezumab 2.5 milligrams and NSAIDs showed a trend for a difference, but was not statistically significantly different. The RPOA type 2 events in both the tanezumab 2.5 milligrams and NSAID groups occurred after the week-24 visit

and closer to the end of the study.

Like the analysis of RPOA type 1 events by study interval I showed you earlier, we evaluated the RPOA type 2 events from Study 1058 in a similar manner. The forest plot on the right provides the risk differences relative to NSAIDs by study interval. As shown in the Kaplan-Meier analyses, the events all occurred after week 24. The risk difference was 0.2 percent or less in all study intervals, indicating the risk differences did not increase throughout the 80-week observation period.

Again, like we did for RPOA type 1, we evaluated the risk differences for developing RPOA type 2 for tanezumab 2.5 milligrams versus NSAIDs in the knee or hip by Kellgren-Lawrence grade. There was a low number of RPOA type 2 events in the tanezumab 2.5-milligram group, with 3 events occurring in the knee and 3 occurring in the hip. There were no Kellgren-Lawrence grade 0 or 1 joints with rapidly progressive osteoarthritis type 2.

When looking at the risk differences, I draw your attention to the Kellgren-Lawrence grade 4 hip

data on the right. The risk difference of 5 percent shows evidence of increased risk. The risk differences for the other Kellgren-Lawrence grades in the knee and hip joints that had RPOA type 2 events were less than 1 percent, indicative of the overall low occurrence of RPOA type 2 with tanezumab 2.5 milligrams.

Another evaluation of joint safety we conducted was an assessment of total joint replacement. Across the treatment groups, over 85 percent of total joint replacements occurred in joints with baseline Kellgren-Lawrence grades of 3 or 4, and over 75 percent of total joint replacements occurred in an index joint. The overall incidence of total joint replacement was similar in the placebo and tanezumab 2.5-milligram group, at 4.5 and 5.5 percent, respectively. Interestingly, the lowest occurrence of total joint replacement occurred with NSAID treatment.

For comparisons of both tanezumab groups to the NSAID group, there was an increased incidence with tanezumab, with the highest rate occurring in

the 5-milligram group. The three sets of bars to the right of the dotted line provide the occurrence of normal progression of osteoarthritis RPOA type 1 and type 2 in the joints that were replaced. A large majority of the joints with total joint replacement were adjudicated as normal progression of osteoarthritis, so the relative distribution across treatment groups is similar to all total joint replacements.

We evaluated joint space width changes to see if there were differences between patients who had a total joint replacement and those who did not, and no treatment differences were noted. For total joint replacements associated with RPOA type 1 or type 2 events, the incidence for the tanezumab 2.5-milligram and NSAID groups were similar. For these outcomes, most total joint replacements occurred in joints that the investigator and patients identified as the index joint.

The overall increased incidence of total joint replacement relative to NSAIDs is primarily

due to more events of normal progression of osteoarthritis that led to a total joint replacement.

We'll now review the risk of total joint replacement by structural severity of the joint. To do this, we evaluated the risk differences for total joint replacement by joint and baseline Kellgren-Lawrence grade relative to NSAIDs.

Across both treatment groups and joints, there were over 3100 joints that were baseline Kellgren-Lawrence grade 0 or 1 at baseline. There were no total joint replacement events identified in these joints. For joints that were Kellgren-Lawrence grade 2 at baseline, the risk difference for knees was 0 percent and 0.4 percent for hip joints. The risk differences increased to approximately 1 percent for Kellgren-Lawrence grade 3 knee and hip joints.

Similar to the pattern observed for RPOA type 2, the largest risk difference for total joint replacement was also observed in hips that were Kellgren-Lawrence grade 4 at baseline, and the

difference was statistically significantly different. The next largest risk difference was for Kellgren-Lawrence grade 4 knee at 4.7 percent relative to NSAIDs.

For the Kellgren-Lawrence grade 4 joints, approximately 85 percent of the total joint replacements in patients treated with tanezumab 2.5 milligrams occurred in index joints and over 90 percent were adjudicated as normal progression of osteoarthritis.

Taken together, these data suggest the risk of a total joint replacement with tanezumab 2.5 milligrams, in comparison to NSAID treatment, was 1 percent or less for joints with Kellgren-Lawrence grade 3 or lower grades at baseline, and was the greatest for Kellgren-Lawrence grade 4 joints.

In summary of my safety presentation, the key findings for the tanezumab 2.5-milligram dose strength are as follows. There was no increased risk of adverse events related to the cardiovascular, renal, or hepatic systems. In

addition, there was no association with increased risk for peripheral or sympathetic autonomic neuropathy, potential drug abuse, dependence, or withdrawal.

The key safety finding for tanezumab was related to joint safety events. The incidence of rapidly progressive osteoarthritis type 1 was increased versus placebo and NSAID treatment. Most events were identified in knees with pre-existing osteoarthritis and did not lead to a total joint replacement.

The incidence of RPOA type 2 was not significantly elevated relative to NSAIDs, with most events occurring in joints with advanced structural severity at baseline. The risk differences for rapidly progressive osteoarthritis relative to NSAIDs were not increased over time.

An association between the occurrence of joint safety endpoints and more severe structural osteoarthritis at baseline was identified. Several data observations suggest the increased risk of joint safety events may be at the joint level

rather than at the patient level.

Lastly, the incidence of total joint replacement was generally higher versus NSAIDs, but the differences versus placebo treatment were not statistically significantly different, and most total joint replacements were associated with adjudication outcomes of normal progression of osteoarthritis and occurs in the index joint.

I will now turn the presentation over to Dr. Anne Hickman.

Applicant Presentation – Anne Hickman

DR. HICKMAN: Thank you, Dr. West.

In this segment of the presentation, I will describe the comprehensive postmarketing risk strategy that has been proposed for tanezumab, focusing on the key components that are outlined in the slides [inaudible – audio gap].

The foundation of our risk minimization strategy is the product label, which will include the U.S. prescribing information, or USPI, and associated medication guide for patients [inaudible] -- risk for rapidly progressive OA and

total joint replacement prominently displayed in a boxed warning.

[Inaudible] as to provide the necessary assurances for safe use of tanezumab, we're also proposing a risk evaluation and patient strategy, or REMS program, with elements to assure safe use that is focused specifically on minimizing the risk of rapidly progressive OA. To support the REMS program, we'll be providing additional imaging for prescribers and radiologists. There is also a comprehensive pharmacovigilance plan, including a safety surveillance study to assess the long-term safety of tanezumab.

Let's begin with the REMS program. The REMS program will ensure that the risk for rapidly progressive OA is minimized and that the incidence of rapidly progressive OA is not increased in real-world use or that seen in studies. In the next few slides, I will describe how the REMS program translates the key risk minimization measures identified in the clinical studies to effective measures in clinical practice.

Briefly, to minimize risk, tanezumab should not be initiated in patients with pre-existing risk factors. Patients without a satisfactory clinical response should stop treatment. Concomitant administration with NSAIDs is not recommended, as chronic use increase the risks threefold, and patients should be monitored for the development of rapidly progressive OA and discontinued if diagnosed.

The cornerstone of a REMS program is education and certification of prescribers, healthcare settings, and pharmacies to ensure that all stakeholders understand the requirements for safe use. Educational materials will be provided to each stakeholder, and prescribers will be required to pass a knowledge assessment test.

The REMS program will ensure that certified prescribers adhere to the monitoring requirements and that patients are counseled. Healthcare providers must report all cases of rapidly progressive OA so that key information can be collected. The REMS program will have a dedicated

coordinating center that will manage implementation and conduct.

The REMS program will ensure that the correct patient initiates tanezumab treatment. Prior to use, patients must be counseled about the risk for rapidly progressive OA and the potential need for a total joint replacement. They will receive instruction on the need to avoid NSAIDs and how to identify them, and the signs and symptoms of rapidly progressive OA and the importance of monitoring to ensure they understand the actions they need to take [inaudible] the risk. They will be instructed to contact their prescriber if they have breakthrough pain or feel the need to take NSAIDs.

Baseline radiographs of the knees and hips will be required to identify and exclude patients with pre-existing, rapidly progressive OA or risk factors. Patients and prescribers must both sign the patient enrollment form, which will document completion of radiographs and document that shared decision making [inaudible] took place.

Prescribers will also attest to their understanding of the REMS requirements, and prescribers will attest that patients meet all REMS enrollment criteria. After these steps, treatment authorization for the first dose can be obtained.

The REMS program will also ensure that safe-use conditions are followed during tanezumab treatment. At each visit, patients should be monitored for signs and symptoms of rapidly progressive OA, and if indicated, repeat radiographs obtained to ensure early identification of joint safety events. Prescribers will be instructed to discontinue patients who do not have a satisfactory clinical response after receiving 2 doses to ensure only patients with positive benefit-risk continue treatment.

Prescriber and patient eligibility will need to be verified and treatment authorization obtained before each dose. Patients should be given a new patient wallet card to remind them of the need to avoid NSAID use.

For patients that continue on treatment, the

REMS program will require annual reassessment of benefit-risk and completion of the patient continuation form. Bilateral radiographs of knees and hips will be required to assess for rapidly progressive OA or risk factors. These radiographs will be very important, as not all patients with joint safety events display clinical signs or symptoms. The radiographs will also provide a new baseline for further radiographic evaluations.

In the next few slides, I will discuss the treatment decision algorithms that we have developed for prescribers to help them understand how to interpret the radiographic findings.

This slide shows the treatment decision algorithm for baseline radiographs. At baseline, the radiograph can either identify the risk factors of concern, as shown on the left side of the tree, in which case tanezumab should not be initiated, or the radiograph can exclude these risk factors, as shown on the right side of the tree, in which case tanezumab could be initiated.

However, as shown in the center tree, if the

clinical findings such as joint pain are discordant to the radiographic findings and a joint safety event such as subchondral insufficiency fracture or osteonecrosis is suspected, an MRI should be conducted to rule out the presence of these factors. An MRI should also be conducted whenever the radiographic findings are equivocal. The MRI findings will then be used to make the final treatment decision.

The treatment decision algorithm for follow-up imaging is almost the same as the baseline, with the exception that now development of RPOA type 1 needs to be considered as well, as noted on the left-side tree. Our treatment algorithms were adapted from those recently published by a scientific expert panel developing treatment decisions for intra-articular corticosteroid injections, as these injections have also been associated with the development of RPOA type 1 and type 2 subchondral insufficiency fractures.

We plan to suggest inclusion of these

diagrams in the educational materials for prescribers. As I mentioned, prescribers will need to monitor for the development of rapidly progressive OA type 1 during tanezumab treatment, and we have developed appropriate tools to enable this evaluation.

In the clinical trials, RPOA type 1 was defined as the loss of greater than 2 millimeters of joint space width in one year. A precise definition was required in order to characterize and objectively quantify the risk. In clinical practice, the objective will be different. Prescribers will need to identify rapid loss of joint space width so that treatment can be appropriately managed.

While measuring joint space width is not customary in clinical practice, joint space width loss can be visually assessed, and loss of joint space width is used routinely in assessing the severity of OA in all current OA classification systems. An example of this is when joint space width is evaluated to determine Kellgren-Lawrence

or KL grade, a classification system that we are proposing for assessment of rapid loss of joint space width.

In 2018, Ratzlaff and colleagues published an analysis of radiographs from the Osteoarthritis Initiative that quantitatively anchored the measured loss of joint space width in medial knees to annual transitions in KL grade. For each KL grade increase in severity, an annual mean decrease in joint space width was determined.

[Inaudible] these data, we have mapped transitions in KL grade that correspond to decreases in joint space width of approximately 1 to 2 millimeters per year, which is somewhat more conservative than our definition in the clinical trials. Therefore, in clinical practice, it can be envisioned that prescribers can monitor for changes in KL grade rather than precisely measuring changes in joint space width to ensure early identification of patients at risk for rapid OA progression.

Let me show you how this would work. This slide shows the decision algorithm for RPOA-1

determination. The KL grade of the baseline radiograph sets the stage for the decision with the follow-up radiograph.

For joints with KL grades of 0, 1, or 2 at baseline, shown on the left side of the tree, RPOA-1 would be diagnosed if there was an annual transition to a KL grade of 3 or higher on the follow-up radiograph. Other KL grade transitions would not be consistent with RPOA type 1. If the KL grade at baseline is 3, as shown on the right side of the tree, RPOA-1 would be diagnosed if there was an annual transition to a KL grade of 4 on the follow-up radiograph.

We have assessed KL grade decisions with data from the knee and hip RPOA-1 cases in the post-2015 tanezumab studies, and we would have correctly diagnosed 100 of the 105, or 95 percent of the RPOA-1 cases correctly.

We acknowledge that there can be difficulties standardizing joint positions with sequential radiographs, and therefore we will be providing suggestions for optimal positioning and

interpretation of positioning on sequential films. It is likely that there will be some false positives and negatives when assessing for rapidly progressive OA type 1, and we will recommend that additional radiographs be conducted if needed to confirm the diagnosis.

We will evaluate the effectiveness of the REMS program and meet its risk mitigation goals, and make appropriate changes if needed. The proposed assessment plan will evaluate both process and outcome indicators from multiple data sources. We'll conduct periodic audits of healthcare settings, pharmacies, and data from wholesale distributors to ensure that all REMS processes and procedures are in place, functioning, and report the REMS requirements.

We will address non-compliance and implement corrective actions if needed. Assessment reports will be submitted to the FDA at 6 and 12 months after approval, and annually thereafter.

To support the REMS program, we'll be providing detailed imaging resources for

prescribers and radiologists that were adapted for real-world use from the imaging materials used for training in the clinical trials. The instructional materials will cover key imaging information that will be important during attainment and assessment of the required radiographs, including definitions and radiographic examples of rapidly progressive OA type 1 and type 2, and risk factors, and will include case studies to demonstrate event progression.

The materials will provide suggestions for serial radiographs and examples of when additional imaging modalities such as CT or MRI should be considered. A radiology request form will be available to ensure that radiologists understand exactly what images are needed and what features they should be looking for. We will have a comprehensive outreach and educational program to ensure access to and uptake of the imaging resources.

We develop the imaging materials with guidance and input from external expert

radiologists, rheumatologists, and orthopedic surgeons, and have currently tested the materials with over 250 potential readers. These physicians and radiologists have indicated that the materials are understandable and could be implemented in their practices.

In addition to minimization of known risks, we will also have a strong pharmacovigilance plan to ensure that we can collect and analyze data on the safety of tanezumab. The plan includes standard adverse event reporting and collection and summarization of safety data from all available sources, including the scientific literature.

For all joint safety events, we'll collect additional information by sending a follow-up form, or as it's commonly known, a data capture aid, to event reporters, both initially and at one year after event occurrence.

In addition, we plan to conduct a long-term, postmarketing safety study that will extend our safety database beyond the duration of phase 3 clinical trials. For the design of the study, we

have proposed a safety surveillance study using real-world electronic healthcare data from the Innovation in Medical Evidence and Development Surveillance, or IMEDS Network, which includes a subset of FDA Sentinel data partners.

The primary study objective would be to estimate the real-world incidence rates of rapidly progressive OA type 2 in patients who received tanezumab and in an appropriate comparison group. We plan to review all the postmarketing safety data in an ongoing basis to ensure that we quickly identify any unanticipated safety findings, including increased rates of joint safety events, and make any needed changes to either labeling or the REMS program.

I will now turn the presentation over to Dr. Alan Kivitz.

Applicant Presentation – Alan Kivitz

DR. KIVITZ: My name is Alan Kivitz, and I speak to you today both from the standpoint of being a clinical researcher, having been involved with tanezumab since 2006, and as a private

practice rheumatologist for the last 39 years, taking care of patients who suffer from arthritis. While I've been compensated by the sponsor to be here today, I have no financial interest in the outcome of this meeting.

I want to bring some of what you've heard today to life by telling you about an actual patient I evaluated recently whose name is Robert. Robert is a 76-year-old male who was referred by orthopedics to our practice to help manage his bilateral knee osteoarthritis of two years duration.

His pertinent history is that he has coronary artery disease having had stents in 2019. His orthopedist actually treated him with a number of appropriate interventions, including NSAIDs before the stent was placed. However, he's now on Plavix, and between that and the CAD history, he would no longer be an ideal candidate to receive further oral NSAIDs.

Intra-articular steroids have been given by his orthopedist and have given Robert some

temporary relief. Intra-articular viscosupplement injections did not give adequate benefit, and I've seen the response to these agents can be variable.

He's already tried physical therapy, which was of some benefit while he was receiving PT. Robert does have an elevated BMI of 35. His Kellgren-Lawrence grade was grade 3 bilaterally, so he does have advanced x-ray changes bilaterally and is symptomatic bilaterally. He was actually scheduled for a total knee replacement in 2019, but it was cancelled when it was found that he needed a coronary stent.

Robert would now like to look at other non-surgical options and he prefers to consider a total knee replacement as a last resort, which was why he was referred to rheumatology. He does not wish opioid therapy, and quite frankly, even if he did, opioids are rather difficult to prescribe in the current environment.

Treatment is always individualized, and part of it could be dependent upon patient goals. With Robert, we need to talk about what worked before

and what has not worked. He already uses acetaminophen, but that doesn't give him enough relief, and viscosupplementations did not work for him, so we would not want to repeat, and insurance wouldn't permit based on lack of response the first time.

We know that steroid injections have given Robert temporary benefit that can always be an option even if short-lived. We can consider so-called NSRIs [ph], but I have found responses can be variable, and some patients have intolerable side effects.

We always have to consider what other comorbidities exist. With Robert, it's cardiovascular disease. For others, it might be decreased renal function or gastrointestinal disease, which prohibit oral NSAIDs. For some, it might be that diabetes or steroid injections have to be given with greater care.

We need to discuss which joints are involved. So is it one knee or both? If it's one knee, we could use something that is more localized

to that knee to get benefit. But Robert has both knees involved, so his treatment plan must take this into consideration.

I mentioned initially that I've been a clinical investigator for tanezumab for more than 15 years. Although the doses we used in the early days were higher than the current doses being presented, the degree of improvement that some patients experienced was unlike anything I've ever studied in my nearly 30 years of performing clinical trials in osteoarthritis.

Of course, we came to recognize with time that some of the risks of treatment occurred, such as rapidly progressive OA, becomes obvious that the benefit and risk of tanezumab needs to be carefully weighed, but physicians are used to doing this for any treatment option.

Going back to Robert, he was open to new possible treatment options, and I think Robert would be an example of an excellent candidate. His treatment options are limited based on what he already tried and failed and also based on his

comorbidities; in other words, his cardiac history. If he had to have a joint replacement, he'd be willing to do so.

The fact that we can avoid major organ toxicities with tanezumab, such as cardiac, GI, renal, and issues with anti-platelet agents, is extremely reassuring for Robert, and would be for patients with some of these other comorbid conditions. For Robert, the potential upside is that he could have enough pain relief to enhance his quality of life.

If we had the option of choosing tanezumab for Robert, we would need, of course, radiographs not just for diagnosis and grading, but also to exclude the presence of any of the pre-existing conditions that would increase his risk for RPOA. We would typically be reviewing and/or updating x-rays as a matter of patient care for identifying exclusionary findings, and KL grading would be incorporated into this radiograph evaluation.

In addition, if Robert were to receive tanezumab, we would also need to do radiographs for

monitoring during treatment. It would be easy to incorporate x-ray into the workflow for tanezumab patients, and Robert will be willing to come back in for a periodic x-ray for monitoring purposes. I would also explain to Robert that if he were to experience any unexpected worsening pain in any of his joints, he would need to contact our office so we could assess whether he would need to come in for further evaluation and possibly further imaging.

Before treating a patient like Robert with tanezumab, we would need to have a conversation about the potential for RPOA and explain that in some instances a joint replacement could be needed. As you've heard extensively, one of the issues that we have to discuss is the regularly use of concomitant NSAIDs.

In Robert's case, between his history of coronary artery disease and use of a blood thinner, he is already aware of the need to avoid NSAIDs. For other patients, of course, we would need to have a discussion about which medications are

NSAIDs, which medications therefore need to be avoided, and this could be supported with supplementary patients' instructions on deciding on such a treatment.

In conclusion, I find as a practicing rheumatologist that there are limited treatment options for patients with OA, and in many ways I have fewer options now than I did several years ago. Having fewer treatment options is also occurring at a time when more of our patients are looking to be able to maintain an active lifestyle as they get older. I view this as a perfect storm of heightened expectations but with fewer options.

Of course, treatment will always need to be individualized based upon shared decision making and patient preferences. Healthcare provider and patient education would be critical, but you have heard some of the strategies planned to help make tanezumab implementation in the clinical setting a reality, and as a rheumatologist, I'm accustomed to REMS programs.

If tanezumab were available, it may not be

an option for everyone, but it could certainly be an option for Robert. Indeed, Robert and I would both embrace its availability.

Thank you for your attention. I will now turn the presentation back to Dr. Verburg.

Applicant Presentation – Kenneth Verburg

DR. VERBURG: Thank you, Dr. Kivitz.

Earlier today, Dr. Schnitzer described the progressive and disabling nature of osteoarthritis and the critical need for new therapies for patients who do not adequately respond or for whom tolerability or safety concerns [inaudible – audio gap] limit the effectiveness.

Tanezumab was developed to treat the chronic pain of osteoarthritis [inaudible] -- tanezumab is not intended for all [inaudible] for patients who are benefiting from these options. The proposed indication is restricted to patients who have had inadequate pain relief and who do not tolerate or are unable to take currently.

The benefit-risk of tanezumab is therefore considered in the context of a population that has

exhausted currently available medical treatment. Of the two dose levels evaluated, tanezumab 2.5 milligrams was associated with the optimal benefits profile in this target population, and the remainder of my presentation will focus on this dose.

All placebeo-controlled studies investigating the tanezumab 2.5-milligram dose level were conducted in patients who [inaudible] commonly used oral analgesic [inaudible]. Studies 1056 and 1057 demonstrate that tanezumab was efficacious in the cohort of patients. Studies 1011 and 1014 provide further support for the conclusion.

There is no single method that is considered optimal to establish patient benefit, so we employed multiple approaches in [inaudible]. The clinical benefit of tanezumab 2.5 milligrams is clearly evident from improvements and physical function and global well-being that were associated with [inaudible] reductions in pain.

Responder analyses for substantial clinical

improvement and sustained improvement [inaudible]. Multi-domain responder analyses, such as the OMERACT and OARSI responder [inaudible], and the efficacy profile in patients with severe symptoms and across demographic, [inaudible] disease severity and geographic subgroups.

Notably, this benefit is seen in a population of patients for whom current treatment was simply not efficacious, not clinically appropriate, or the patient is unwilling [inaudible].

As we reviewed earlier today, tanezumab 2.5 milligrams provides clinically important improvement in the target patient population. Significant improvement was across all of these responder [inaudible], and the numbers needed to treat to achieve the clinically important outcomes [inaudible] -- placebo was replaced by tanezumab 2.5 milligrams, ranged from 7 to 10, for a mean of [inaudible]. [Inaudible] to treat was 6 for these same outcome measures [inaudible].

Tanezumab lacks the risk characteristic of

NSAIDs and opioids due to a mechanism of action that is distinct from either of these [inaudible] classes. NSAIDs have been associated with adverse cardiovascular outcomes; upper gastrointestinal ulcer complications; and adverse cardiorenal effects, among others. Serious risks associated with opioid use are also well known and, of course, include addiction and overdose. Thus, in keeping with our target population, [inaudible] 2.5-milligram benefit [inaudible] appropriate.

As Dr. West indicated, the most significant risk identified with tanezumab 2.5 milligrams was isolated to adverse joint safety outcomes. In the post-2015 evaluations of joint [inaudible] carried out in patients with advanced osteoarthritis, as indicated by the degree of structural joint damage of the index joint at baseline, the number of patients with osteoarthritis involving multiple joints [inaudible] -- the medical history of approximately 10 percent of patients, a hundred were in a total joint replacement prior to study entry.

In this patient population, rapidly progressive osteoarthritis type 1 that was observed with both tanezumab 2.5 milligrams and NSAIDs was greater with tanezumab treatment. Rapidly progressive osteoarthritis type 2 was also observed in both treatment groups. The incidence of total joint replacements ranged from 5.5 percent with tanezumab 2.5 milligrams and 2.6 percent for NSAIDs. The incidence in placebo-treated patients was [inaudible] 4.5 percent.

Nearly 9 of every 10 total joint replacements occurred in patients [inaudible] to normal osteoarthritis progression; 77 percent occurred in [inaudible]. Neither tanezumab 2.5 milligrams nor NSAIDs were associated with general or systematic acceleration of osteoarthritis progression. Over 96 percent of patients [inaudible] treated with either agent were not affected by one of the adjudicated composite joint outcomes.

Finally, the risk of an adverse joint outcome is typically isolated to a [inaudible]

single joint [inaudible] even within an affected patient.

Similar to the assessment of benefit by numbers needed to treat and numbers needed to harm, [inaudible] for the principal joint safety risk associated with 2.5 milligrams. The number needed to harm to observe one additional patient with rapidly progressive osteoarthritis type 1 or type 2, [inaudible], as shown in the left panel, or NSAIDs, as shown in the right panel.

Within each adjudication outcome, the data are presented separately from [inaudible]. A different pattern exists for rapidly progressive osteoarthritis type 1 compared to type 2. For type 1 events, the number needed to harm is lower for knee joints relative to hip joints; whereas for type 2 events, the numbers needed to harm are the same for knee.

The numbers needed to harm for any total joint replacement, and those specifically associated with rapidly progressive osteoarthritis type 1, type 2, or normal progression of

osteoarthritis, are now shown below the dotted line. The numbers needed to harm for an outcome of total joint replacement associated with either rapidly progressive osteoarthritis type 1 or type 2 are estimated 500 or higher in comparison with placebo [inaudible].

Most total joint replacements occurred in joints with an adjudication outcome of normal progression of osteoarthritis as reflected by the lower numbers needed to harm, shown for this outcome alone, and the similar values for the category of any total joint replacement.

Comparison of the numbers needed to treat to the numbers needed to harm with tanezumab 2.5 milligrams [inaudible] is one line of evidence to support the conclusion that the benefit-risk [inaudible] profile of this dose is favorable. Comparison of the number needed to treat to the number needed to harm is most favorable for rapidly progressive osteoarthritis type 2, followed by type 1, then total joint replacement.

The numbers needed to harm to observe one

additional event of rapidly progressive osteoarthritis type 1, type 2, or total joint replacement [inaudible] 2.5 milligrams, versus NSAIDs, now shown in the left panel, are put into perspective by the numbers needed to harm when an opioid replaces a non-selective NSAID, shown in the right panel. These numbers needed to harm associated with opioids were reported in a 2010 [inaudible] patients.

Numbers needed to harm to observe one additional adverse joint safety outcome with tanezumab appear to be favorable in the context to the numbers needed to harm for serious adverse outcomes [inaudible] opioid treatment. To further contextualize the joint safety events with opioid-related risks, the incidence of total joint replacements and rapidly progressive osteoarthritis type 1 and type 2 with tanezumab 2.5-milligrams are shown now in relation to estimates of opioid abuse alone or opioid abuse [inaudible].

As depicted by the solid magenta bar, the point estimates for the incidence of opioid abuse,

or abuse and dependence combined across multiple data sources [inaudible], range from 1.3 to 11.3 [inaudible]. And as shown by the point estimates with a 95 percent confidence interval, the incidence of joint safety events associated with tanezumab 2.5 milligrams were of similar magnitude.

This comparison suggests that the magnitude of joint safety events associated with tanezumab 2.5 milligrams is acceptable in the context of opioid-related toxicities. Of course, an important consideration beyond the magnitude of the risks are the different clinical consequences [inaudible] of the adverse outcomes associated with [inaudible] tanezumab or opioids.

As one example, tanezumab-associated total joint replacements occurred primarily in index joints that is the most painful or problematic to the patients that were KL grade 3 or 4 at baseline and associated with normal osteoarthritis progression, as would be anticipated with [inaudible] osteoarthritis.

The overall conclusions drawn from our presentations today are as follows. If approved, tanezumab will be the first in a new pharmacologic class of pain therapy, as a mechanism of action that is distinct from that of NSAIDs and opioids, and is devoid of risk of abuse, addiction, or overdose, and other serious safety concerns associated with [inaudible] opioid or NSAID use.

Tanezumab addresses a significant unmet medical need in the treatment of osteoarthritis. Specifically, it is targeted to patients in [inaudible] whom other analgesic medications are inadequate or not appropriate.

The benefit-risk balance of tanezumab 2.5 milligrams subcutaneously is positive in the context of the unmet medical need for patients with osteoarthritis, the efficacy and safety profile of tanezumab's [inaudible] patient population intended for tanezumab treatment, and the proposed risk management plan.

Finally, the weight of evidence supports approval of tanezumab 2.5 milligrams within the

current therapeutic context of managing patients with osteoarthritis. Thank you for your time and attention. This concludes the sponsor's presentation.

Clarifying Questions

DR. SUAREZ-ALMAZOR: Thank you.

We will now take clarifying questions for Pfizer. Please use the raised-hand icon to indicate that you have a question, and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter.

If you wish for a specific slide to be displayed, please let us know the slide number if possible. And finally, it would be helpful to acknowledge at the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member. We are running a little late, so this part of the session is really for clarifying questions. Discussion points can be

left for tomorrow

I would like to start by asking a question from Dr. West related to safety. It's clear that tanezumab is efficacious, however, the benefits are modest. So it's likely that patients may require other analgesia while they are taking or they are receiving this agent.

NSAIDs are not recommended, so I was wondering if there are any data on the safety on the joints with concomitant use with other modes of modes of analgesia, such as acetaminophen, opioids, or corticosteroid injections.

DR. WEST: Yes. We have looked at the concomitant use of various medications. First, with acetaminophen, that was actually the rescue medication utilized in our clinical trials. Many patients -- most patients actually, to clarify -- used acetaminophen, and we did not see any increased risk or any association with the use of acetaminophen in joint safety events.

Intra-articular corticosteroids were not to be used during this study, although there were some

patients who did utilize those. Our numbers are low, but we did not necessarily see any increase there as well.

With respect to opioids, we have limited information, but in the pre-2015 studies, we did conduct two long-term extension studies in which patients could use standard-of-care medication. So we have some experience there, and again did not see an association with the concomitant use in joint safety events.

DR. SUAREZ-ALMAZOR: Thank you.

Dr. Meisel?

DR. MEISEL: Thank you. Steve Meisel with Fairview in Minneapolis. I've got a question for Dr. West and a follow-up question for Dr. Hickman.

Dr. West, I think you mentioned this, but I'd like some additional clarity. For the rapidly progressing arthritis, if somebody had arthritis in whatever, the left knee, but the right knee was normal, did you see any rapidly progressing arthritis in an unaffected joint, or is it only in the affected index joints?

DR. WEST: Correct. We had one patient with RPOA type 1 in the 2.5-milligram dose who had two affected joints; so that's out of all of the patients treated. We did do an analysis of the change in joint space width in the affected joint with the rapidly progressive osteoarthritis versus the contralateral knee, and we did not see the changes in joint space width in the contralateral knee that were observed with the RPOA-1 type knee.

DR. MEISEL: So the RPOA-1 was only in the originally affected joint, if I'm hearing you correctly. Is that right?

DR. WEST: Correct, with respect to looking at those changes, yes, in joint space width.

DR. MEISEL: Okay.

DR. WEST: And we've evaluated a variety. We do think it's a joint-level risk profile as opposed to a patient-level risk profile, based on the data we've been able to evaluate.

DR. MEISEL: Then a follow-up question for Dr. Hickman in terms of the REMS and the follow-up x-rays, are you proposing that all joints be

examined at the intervals that you propose or only the originally affected joints be examined?

DR. HICKMAN: Yes. Thank you. For the REMS program, what would happen would be at baseline, and if the patient continued beyond one year, those radiographs would be of both knees and both hips. So that would screen out for any of those joints having RPOA pre-existing or developing a risk factor.

Now, at any time for cause, though, we're recommending that if there's pain or swelling -- and that was the most common adverse event that we saw in the trial. About 30 percent of patients with RPOA had pain or swelling. If we see those type of events, we're asking prescribers to monitor that at each visit; then we're requesting that they do repeat radiographs of the affected joint if it's indicated, based on their physical exam.

DR. MEISEL: Okay. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Griffin?

DR. GRIFFIN: Yes. Thank you. Marie

Griffin from Vanderbilt. My question is also for Dr. West. I'm a little bit confused about normal progression of OA. I know these were half the events but were not the primary outcomes. But I don't think we ever saw those results of normal progression of OA, which is what leads most to a joint replacement by exposure group.

Do you have those results?

DR. WEST: Yes, we do have that summary. And it is fairly similar to what we see with the total joint replacement because that is what we see most commonly associated with total joint replacements.

DR. GRIFFIN: Again, the exposure groups were more likely to have normal progression of OA than placebo?

DR. WEST: Relative to placebo, we did not see much difference because those were fairly similar. The difference, really, for normal progression of osteoarthritis was relative to the NSAIDs, where we saw some differences in that regard.

DR. GRIFFIN: Are you putting that slide up or you don't have that?

DR. WEST: I apologize. We do have the slide. I can't get to the number. I can tell you the number, though.

As far as the numbers of patients, there were 31 total NSAID patients who had normal progression of osteoarthritis. Again, you have to consider the denominator; so in 108, in the 2.5 milligram out of 1500 patients, and the placebo then were 24 out of 514. But I apologize. We will get the slide and show that in a few moments, please.

DR. GRIFFIN: Okay. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Nason?

DR. NASON: Thank you. I have a couple related questions for Dr. West. I'll actually start with one that's related to the question that was just asked, which on one slide you mentioned there were people where physicians determined whether they were normal OA or rapid progressive OA. And I was wondering, how many of those people

and whether they're included by default for the normal OA slide compared to the previous question, or if they're just excluded for the difference.

I have a couple more questions, but that's one, if you'd like to answer that.

DR. WEST: First, let me show JS-199, and it will give all the numbers. And the last question, I think it relates to what you also are asking. This is taken from an incidence perspective. It's 5.3 percent versus 2.7, and 4.3 was the placebo treatment group.

Could you restate your question? I apologize. I didn't quite capture what you were asking me.

DR. NASON: Sure. One of the slides said that there were some people for whom it was ambiguous whether it should be considered rapidly progressing OA or normal OA. And I was wondering if those people are included, then, as normal OA, or how those people are included in these analyses.

DR. WEST: No. They're not included. But there were only 2 patients out of the 451 in which

the committee was not able to determine rapid from normal progression. We did a sensitivity analyses, and obviously with 2 patients there wouldn't be much impact. But there was no impact.

DR. NASON: Okay. Thank you. That's helpful.

My next question is about the definition of RPOA type 1. I believe you used 2 millimeter or greater change as your definition, but is everyone in the study at risk of that? I mean, if you didn't have an eligibility criteria that stated that they must have at least 2 millimeters of space, for instance, at the beginning, it would seem that they would not be able to qualify for that definition. And similarly, I don't know if people who'd had, for instance, a total joint replacement in the past in that joint would be able to qualify.

So if there's a substantial number of people who are not able to show RPOA type 1 by that definition, it would make it hard to interpret the actual percentages that do.

DR. WEST: So you're correct. Kellgren-Lawrence grade 4, those patients were allowed to enroll, and many of those, in most cases, would have less than 2 millimeters on joint space width, so they would not meet that definition.

However, if we could show slide JS-716, please, we did look at changes in joint space width. This is showing you categorical changes. These are just baseline Kellgren-Lawrence grade 4 joints from Study 1058. So this is the 56-week treatment period with the 80-week, and then 24 weeks off treatment.

We're comparing the 2.5-milligram dose group to NSAIDs, and this is total numbers of joints with baseline Kellgren-Lawrence grade 4. So these would be the ones you're talking about that wouldn't necessarily be able to qualify for RPOA type 1. And you can see that the profile, the changes in joint space width, you can see there's not a lot there to lose. But it's about minus 0.5, and there's really not any difference between the tanezumab and the NSAID treatment group. So while

they're not accounted for in RPOA type 1, we didn't see any particular differences from either perspective. Slide off.

DR. NASON: Were those people excluded or just listed as not having the event for the Kaplan-Meiers and the analysis of the RPOA-1 event rates?

DR. WEST: They were not in the RPOA type 1 event rate, no, because they would not have met the criteria with the 2-millimeter change.

DR. NASON: Right. Sorry. Were they in the denominator? So were they included in the sort of at-risk group for the Kaplan-Meiers or the percentages?

DR. WEST: I would have to clarify that. I believe that those patients are included, but I would have to clarify that; if we can get back to you with a firm answer on that.

DR. NASON: Sure. And I think if they were included but were not at risk, it might be useful if you were able to show the rates, and the risk difference, and maybe even the Kaplain-Meiers

without them included, since they're not possible to have that particular outcome.

DR. WEST: Okay. Thank you. We will discuss that and get back to you on that. Thank you.

DR. NASON: Okay. I guess the last thing I'd like to ask quickly is I believe also you couldn't have type 1 and type 2 and a TJR. Those are exclusive endpoints; correct?

DR. WEST: No, they're not. Within the adjudication outcomes, for the primary composite endpoint, we did have a hierarchy, so a patient would contribute one to the primary composite endpoints. However, the analyses of individual endpoints, the components of the primary composite, a patient could contribute more than one endpoint, and all patients were considered in the total joint replacement analyses irregardless of their adjudication outcome.

I would point out also with, again, the 2.5-milligram group, there's only one patient who had a component that is in the primary composite

endpoint. There's only one patient who had 2 joints affected, both RPOA type 1.

DR. NASON: Okay. So they could have more than one, but not in the same joint then, to have the different outcome.

DR. WEST: Right. So in your example, RPOA type 1 and RPOA type 2, for the primary composite endpoint, they were counted one, but they would have been counted in both individual type 1 and type 2 analyses.

DR. NASON: Okay. I was going to ask if they were censored out of the other -- for the component analysis, then, if they were censored or how they were handled if they had type 1, but I guess they could be still at risk of the other type. I think that's what you're saying.

Did you show a Kaplan-Meier for the composite outcome? I'm afraid I missed it if you did.

DR. WEST: No, I did not. It looks very similar to the RPOA type 1, since about 70 percent of the events are RPOA type 1.

DR. WEST: Okay. Alright. Thank you. I'll stop and let someone else ask questions.

DR. SUAREZ-ALMAZOR: Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I have a question for Dr. West, Christine West. On subgroup analysis, given that OA is more common in women, and blacks, and Hispanics, more so than with white men.

Did you show us the subgroup analysis on those?

DR. WEST: No, I did not show you the data.

If we could show slide JS-823, we did do a large number of subgroup analyses to assess the potential impact of a variety of baseline characteristics, and then post-baseline responses. So that's what is being shown on this particular slide. You can see the different things that we evaluated; many things within each of these categories.

After doing these analyses, again, the only thing that came forward as being an association was the structural severity of the joint at baseline.

And this is one of the reasons that we have concluded that we feel that the risk is at the joint level as opposed to the patient level, because many of these characteristics that would be at the patient level showed no association, and then when we look at changes within the joint, we saw those isolated to the affected joint.

MS. ROBOTTI: I did hear you say that, but I just wanted to be perfectly clear because it didn't seem likely.

You had a slide, MA-68, which I saw something on it. And I didn't actually get to look at it long enough to really make sure that I had a clear question, but could we see it again? I think in there, it says 85 percent of joints did not have TJR -- events, most often in the majority, 85 percent of affected joints did not.

Is there a way to separate that out to see which joint was more likely to get TJR when it was on tanezumab, the drug?

DR. WEST: Yes. We did do analyses based on that. And just to clarify, the 85 percent with no

total joint replacement is for the RPOA type 1 event. So that's where we do see a distinction between type 1 and type 2. Actually, with the 2.5-milligram dose strength, [inaudible – audio gap] percent of patients ended up having a total joint replacement, as opposed to RPOA type 2, it's closer to 50 percent. So there definitely was a difference in that regard.

If we could show slide MA-101, I can address your question a little bit more about the knee and hip differences. This is showing on the left, as you can see, the knee joint, and on the right, the hip joint. We looked at this based on the structural severity of the joints, so you can see that the risk increases more when you get to those that are closer to end-stage OA with Kellgren-Lawrence grade 4 OA.

Another point that we've actually looked at is when we subset this into the index joint versus the non-index joint -- so the index joint being the one that the patient has identified with the investigator to be the one that they actually

sought treatment for in the study -- we see that most of those TJRs are occurring in that index joint as opposed to the non-index joint. Slide off.

MS. ROBOTTI: Great.

Last question for Dr. Hickman, please. In the REMS, it requires biannual radiographs, which do have a low but cumulative effect, cancer, radiation. Is there any significant risk over time, if somebody takes this drug for 4, 5, 20 years, of having biannual radiographs?

DR. HICKMAN: Thank you for the question. We think that the risk would be low. That's one of the reasons we're only requiring the radiographs to occur annually. I'm certainly not an expert in that type of risk.

I don't know if, Dr. Carrino, you might have a better idea of the radiographic type of risk.

MS. ROBOTTI: Because you are doing both hips and both knees every time.

DR. HICKMAN: Right, annually; yes, once a year.

DR. CARRINO: Yes. Hi. It's John Carrino, professor of radiology at Cornell, and vice chairman of radiology at Hospital for Special Surgery in New York. While I have been compensated by the sponsor to be here today, I have no financial interest in the outcome of this meeting.

So the question relates to radiation risk and the risk of carcinogenesis. With doing projection radiography, you would be most concerned if there was a potential -- a critical organ; so let's say in the pelvis, the gonad. And if we're talking about the adult population -- not a pediatric population, adult population -- baseline risk for cancer for all of us is about 20 something percent. And if we're using high radiation techniques like CT, it increases it a fraction of a percent, like 0.5.

So these are low radiation techniques. So the increased risk of carcinogenesis conservatively would be a fraction of a percent less than 0.5, just off the top of the head, but I think it would be far lower than that. I think from a clinical

standpoint, we certainly do radiographs on patients yearly for certain things. Particularly if they get an arthroplasty and they undergo a surveillance, there's often surveillance radiography that's done yearly, so they would be in that category.

So in general, no substantially increased risk for carcinogenesis, based on the radiographic paradigm suggested.

MS. ROBOTTI: Okay. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Richards?

DR. RICHARDS: Hello. John Richards, VA Pittsburgh.

For Dr. Verburg, were patients with chondrocalcinosis in their knees or hips included in the study, or was that an exclusion criteria? That's the first question.

The second one is about comorbidities. Do you have any information about comorbidities that were allowed for the patients, specifically diabetes, kidney disease, and presence of neuropathies, radiculopathy from associated spinal

disease, or other neuropathies? Thank you.

DR. VERBURG: Sure. Apologies. Could you just repeat your first question? I just lost it.

DR. WEST: I think chondrocalcinosis.

DR. VERBURG: Hello? Oh, chondrocalcinosis. Thank you for that.

Yes. Patients who had crystal arthropathy, or any evidence of a pre-existing condition that would either confound or perhaps was a precursor for rapid acceleration of osteoarthritis, were excluded from the clinical trials.

In terms of enrollment of patients with comorbidities, yes, patients with diabetes were allowed to enroll in the trial as long as they were reasonably well controlled, as were patients with varying degrees of EFR or kidney function. The only patients that we excluded were patients with severe renal [inaudible – audio gap]. What we saw, basically, is about probably half or so had cardiovascular risk factors for [inaudible], as such, including hypertension, diabetes, and other factors like that.

I'm happy to amplify on that if you need more information.

DR. SUAREZ-ALMAZOR: Dr Honczarenko?

DR. HONCZARENKO: Thank you. Marek Honczarenko. I have two questions. Question number one is related to potential analyses, which you did for predictive biomarkers of adverse events in order to increase or improve benefit-risk ratio.

I'm just curious if you did any type of genetic analysis, especially the polymorphisms of NGF or NGF receptor pathways. We have, really, very interesting examples of variants; for example, MCF2L, which is associated with osteoarthritis to regulate the NGF pathway. Considering the low incidence of the rapidly progressing OA, which you have observed in your studies, these types of genetic polymorphisms are incredibly interesting candidates for predictive biomarkers.

The second question is, in your analysis, did you analyze end of phenotypes; for example low, medium, or high pain intensity groups, or pain intensity groups, which people who experience pain

with neuropathic features refer to pain or pain localized to a joint?

DR. VERBURG: Thank you for the question. This is Ken Verburg. We have not done any genetic testing to look for associations with adverse joint safety outcomes. So thank you for that suggestion. We just haven't had an opportunity to do that yet.

I will say that one of the biomarkers that was employed, that Dr. West described in her presentation earlier today, was MRIs. Now, we did not use MRIs to determine eligible patients, but the MRI features in a retrospective analyses I think are fairly interesting with regard to their predictive value, or lack thereof, for an adverse joint safety outcome. That I think answers that question.

Your second question was have we evaluated pain relief, the effects of tanezumab, in patients with varying degrees of baseline pain or physical activity disability, if you will; and the answer to that is yes. In particular, of course, we focused a considerable amount of attention to the severe

symptomatic cohort, so these would be patients that had pain scores above 7, physical function scores above 7, and global assessments of poor or very poor.

We see a very robust profile there in terms of efficacy. The placebo response, as you might anticipate, is a little bit larger than it is in the moderate symptomatic cohort, but the treatment differentials are about the same. So across the spectrum of patients with osteoarthritis symptomatic severity, we see tanezumab 2.5 milligrams as relatively stable.

DR RICHARDS: Thank you.

DR. SUAREZ-ALMAZOR: Dr. Cheng?

DR. CHENG: Hi. Ed Cheng from Minneapolis. Thank you very much for the sponsor's presentation. I have many questions, but I'll limit them to the methodology and the safety pretty much. Methodology, I suppose, is with Dr. Verburg.

For the clinical studies that you'd mentioned, both before and after 2015, I didn't see anything mentioned regarding the follow-up

completion of patients enrolled on these trials. Then for the patients that were enrolled, this was all forms of the DJD or osteoarthritis? What about secondary forms related to hip dysplasia; osteonecrosis; tenosynovial giant cell tumor; rheumatoid arthritis, post-traumatic; in these scenarios?

Could you address that, please?

DR. VERBURG: Sure. I'll take the last one first. Yes, those patients would have been excluded. So patients who met ACR clinical and radiologic criteria for a diagnosis of osteoarthritis were included. But those that may have had other ideologies associated with their osteoarthritis -- sorry. I've spaced your first question. Could you repeat that question?

DR. CHENG: The percent of patients completing their follow-up in the studies before and after 2015; how many completed the follow-up?

DR. VERBURG: In the pre-2015, yes -- I apologize. In the pre-2015 period, there was no extended treatment or follow-up period following

discontinuation, basically, on the order of 8 to 6 weeks. In the post-2015 period, of course we included a 24-week follow-up period for the three studies.

I wonder if I could -- I don't know what those percentages were, so I'm going to reach out to maybe our lead statistician, Dr. Glenn Pixton, and see if he has an idea of what that completion rate was to the follow-up period.

MR. PIXTON: Sure. Glenn Pixton, Pfizer statistics. In our three post-2015 OA studies, there were about 75 to 85 percent of patients who completed that 6-month follow-up period.

DR. CHENG: I'm sorry; 75 to 85 percent met the 6-month follow-up period, but some of these went much longer than that, like Study 1058 I think. Did they all reach the last endpoints, study endpoint?

MR. PIXTON: I was referring to the post-treatment, follow-up period. About 75 to 85 percent of patients completed the post-treatment, follow-up period whether or not

they completed the treatment period, if that makes sense.

DR. CHENG: I see. So we only have knowledge, then, on about three-fourths, the 85 percent of patients, on 6 months after treatment. That's the limit of our knowledge on this drug.

Do I understand you correctly?

MR. PIXTON: Correct. There were only 5 to 10 percent of patients that did not enter the follow-up period at all. So the difference between those numbers includes patients who had at least some follow-up period before they discontinued follow-up.

DR. CHENG: Okay. So the longer term effects after 6 months, we don't know what their impact might be.

MR. PIXTON: Yes. The studies were planned to end 6 months post-treatment, generally.

DR. CHENG: Okay.

Then just a couple questions for Dr. West. I think that pertained to safety. Just to expand

on the previous point made, I think you made the statement that this is a joint effect rather than a patient side effect because one of the patients with the contralateral knee did not show evidence of that as severely. But I think more accurately, you didn't look at other target/non-target joints other than the contralateral knee; for example the ipsilateral hip, the shoulders, the elbows.

Is that correct?

DR. WEST: No, that is not correct. What I was referring to during my presentation was the contralateral joint for the RPOA type 1 patient. But we actually evaluated -- we had Kellgren-Lawrence grades on all hips and knees at baseline, and those radiographs were [inaudible - feedback] throughout the course of the study and evaluated by the central reader to surveil for joint safety events. So we saw a low occurrence in Kellgren-Lawrence grade 0 or 1 event.

If we could show slide [inaudible - feedback] -- I'm not sure -- the audio was making a funny noise. I don't know if we heard JS-735,

please.

This is showing the Kellgren-Lawrence grade 0 joint across all three of those osteoarthritis subcutaneous studies. You can see the number of joints of the patients who had at least one Kellgren-Lawrence grade 0 joint, and then the occurrence of joint safety events within those Kellgren-Lawrence grade 0 joints.

So you can see 0.2 percent or 2 patients who had a Kellgren-Lawrence grade 0 had a RPOA type 1 event and no total replacements or RPOA-2 in any Kellgren-Lawrence grade 0 joints.

DR. CHENG: Okay. I guess maybe more specifically, surely in the clinical scenario, we see patients with more severe disease in multiple joints at, say, KL grade 3 or 4 in more than one joint; perhaps a knee and a hip, or 2 knees, or shoulder and hip, or what-have-you.

The impact of the RPOA that you spent a lot of time talking about, does that occur in the non-targeted joint as well? That's what I'm wondering. If someone has severe hip arthritis and

knee arthritis, and you gave this for the knee, was RPOA detected in other joints, the non-target joints? Because it may be related to more severe disease, as you're, I think, alluding to.

Is that correct?

DR. WEST: Correct. But we still did see a difference between the index joint and the non-index joint. So there were some occurrences more so with the 5-milligram dose strength than with the 2.5-milligram dose strength.

I would like to bring up -- I'll be able to show you some additional data. If we can show slide JS-743, please? This is showing you the hip and knee joint by severity with Kellgren-Lawrence grade; and you can see that with the lower grades, again, there is not as much changes in the risk difference or time.

If we also could please bring up slide JS-752? We'll look here at index versus non-index, which is getting more specifically to your question. This is for the hip joint versus placebo. You can see a difference if you focus on

the KL grade 4 or even the 3, to your point about patients who have multiple joints. And many of these patients did have multiple joint involvement, but there was a difference.

So the patients we could detect events, whether it was targeted as an index or not, as you can see from the right-hand side, those are the non-indexed joints. It did appear, based on multiple analyses, whether of the knee and the hip, that there did appear to be increased risk in the joint that the patient declared to be their index joint as opposed to that that was not.

So whether that's a difference we're seeing, as is well known, not necessarily does radiologic severity match up with symptomatology, since patients, particularly with the total joint replacement, have multiple factors factoring into when they make that decision to go to surgery. Slide off, please.

DR. CHENG: Okay. So to clarify, as this is a systemic drug, since you're giving it subcutaneously after 2015, it may have similar,

both beneficial and side effects, profiles for multiple joints, not just whatever the patient declared was the target joint if they have two diseased joints. That's my understanding.

DR. WEST: Yes, I agree. The potential is there, although we see that the more symptomatic joint seems to occur more commonly in the more severely symptomatic joint, and it is associated with severity of the joint.

So those joints that are KL 0 and 1 appear to be much lower risk. And as you move up the severity scale, there seems to be some increased risk; again, more so with it most being shown in Kellgren-Lawrence grade 4 hip.

DR. CHENG: Alright. So it is the systemic drug, though. Okay.

Just to shift gears for a second here then, the risk of the nerve growth agent --

DR. SUAREZ-ALMAZOR: Dr. --

DR. CHENG: -- hello?

DR. SUAREZ-ALMAZOR: Yes. Dr. Cheng, we're going to need to move on --

DR. CHENG: Can I just get my last question in?

DR. SUAREZ-ALMAZOR: Very quickly, please, because we're already late, and there are a number of people who also have questions. Thank you.

DR. CHENG: Okay. Very quickly, then.

Dr. West, there are CNS effects of nerve growth factor in the cortex and basil ganglia. So I'm wondering did you study the CNS risk of tanezumab. Many of these patients are elderly, they have dementia, or they're pre-dementia. Was this assessed? I'm just wondering. You never talked about any of the CNS effects.

DR. WEST: Yes. Thank you for the question. I'd actually like to ask my colleague, Dr. Mark Brown, to address this, as he focuses on the neurological safety.

DR. BROWN: Thank you, Dr. West.

This is Mark Brown from Pfizer clinical development. Tanezumab, as was noted in the presentations, is a large immunoglobulin protein, which is typically not able to pass across the

blood-brain barrier to gain access into the central nervous system. And in some of our non-clinical studies, we've actually shown that a very small fraction, something on the order of 0.05 percent, of tanezumab is able to gain access into the CSF in non-clinical studies.

We actually looked at CNS-related adverse events within our tanezumab clinical control trials, and we found that the rate of CNS-related adverse events was quite low. The most common of these was headache; the next most common was dizziness. But when you look at these at exposure incidence of adjusted values, these were comparable to placebo in terms of their incidence. So we did not really have evidence that there was a CNS-related activity of tanezumab.

DR. CHENG: Okay. Well, we can discuss it further. Thanks very much.

DR. SUAREZ-ALMAZOR: Okay. We are only going to be able to get one more question because we're running late. But when we come back, if there is time, we can have the other people who

raised their hands ask their questions.

Dr. Katz?

DR. KATZ: Thank you. Lee Katz, New Haven, Connecticut. I have a question for Dr. West. It's actually several parts.

You commented during the presentation that radiographs were taken of the hip, the knee, and the shoulder, but I didn't really see you present any of the data from the shoulder. And since it's a non-weight-bearing joint as compared to the other two target joints, I was wondering if you could review the underlying baseline osteoarthritis, whether these patients progressed to advanced osteoarthritis.

There were a couple of patients that went on to rapidly progressive osteoarthritis. And finally, did any of these patients undergo a total joint replacement? Thank you.

DR. WEST: Just to clarify, you're referring all to the shoulder; is that correct?

DR. KATZ: Yes. You said radiographs were taken of all those three joints, but you never

really presented any of the shoulder data. You did say that a couple of the patients went on to rapidly progressive osteoarthritis. But from your data, the shoulder is a non-weight-bearing joint and would have more of a systemic effect as opposed to a weight-bearing effect.

So I'm wondering if you could present the shoulder data as to their baseline osteoarthritis; did they progress in their osteoarthritis; progression to rapidly progressive osteoarthritis; and finally, did any of those patients have to undergo a total shoulder replacement?

DR. WEST: Okay. Please show slide JS-671, and that will address almost part of your question, and then I will continue to provide additional information.

This is not showing all of the adjudication outcomes, but you can see in the last row on this particular table it shows patients who had osteoarthritis identified in their baseline radiographs, the occurrence of event, rather it be rapidly progressive OA type 1 or normal progression

of OA.

So you can see there was one in the placebo patient, the placebo treatment group, a similar percentage with RPOA type 1 in the 2.5-milligram dose group. We did see more involvement with the 5-milligram dose group.

The data that are not included on this particular slide is RPOA type 2, and there were actually 2 patients who had RPOA type 2 develop in the shoulder. One was in the 5-milligram dose group and one was in the NSAID treatment group, and both of those patients did have total joint replacements in their shoulder, their affected shoulder. We did not see any total joint replacements occurring in the shoulder for patients in the 2.5-milligram dose group. Slide off, please.

I'm not sure. But I think I addressed all of the questions. Did I miss anything?

DR. KATZ: No, I think you did. I'm just wondering, we really didn't describe the degree of osteoarthritis of the shoulders that the patients

had, so we don't really know what their classification was at the beginning of the study and as it's going through. You did it for the knee and the hip, but you have the data I assume for the shoulder. So maybe later on this afternoon or tomorrow, you could present that data.

DR. WEST: Yes. I can tell you about 10 to 15 percent, based on the central reader's assessment of the shoulder radiograph. So you're right; we didn't because there's not a scale similar to Kellgren-Lawrence grading. But we did have the musculoskeletal radiologists assess the shoulders at baseline for the presence of osteoarthritis, and about 10 to 15 percent across the treatment group had osteoarthritis evident in their shoulder at baseline.

So that is characteristic of the population, then I was showing you the outcome for those patients, whether they had OA at baseline in their shoulder or not.

DR. SUAREZ-ALMAZOR: Okay. Thank you.

We will now break for lunch. We will

reconvene again in 45 minutes at 1:30 Eastern Time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin at around 1:05 to ensure you're connected before we reconvene at 1:30 p.m. Thank you.

(Whereupon, at 12:45 p.m., a lunch recess was taken.)

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

(1:30 p.m.)

DR. SUAREZ-ALMAZOR: We will now proceed with the FDA presentations starting with Dr. O'Donnell.

FDA Presentation – Mary Therese O'Donnell

DR. O'DONNELL: Good afternoon. My name is Mary Therese O'Donnell, and I'm the clinical reviewer in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine, who participated in the review of efficacy data provided in the tanezumab BLA application.

The applicant has presented the study designs and emphasized the top-line result that it feels are most relevant for your consideration today. My presentation is designed to be brief because many of the key efficacy findings are not refuted.

I will start with a discussion of why the clinical team has focused on the so-called post-2015 studies. Dr. Pokrovnichka will cover this in greater detail when she presents her review

of safety. Finally, I will put the treatment effect size observed in the tanezumab clinical trial into context with other approved osteoarthritis therapies. And lastly, I will discuss the strengths and limitations of the health technology assessment presented in the applicant's briefing documents.

From the perspective of efficacy, there are several reasons to support our focus on the post-2015 studies. These studies contain the majority of the data on the proposed tanezumab dose of 2.5 milligrams every 8 weeks, the subcutaneous route of administration, and the patient selection criteria that were designed to support the indication proposed for a restricted osteoarthritis population for whom the use of other analgesics is ineffective or not appropriate. Last, some of the pre-2015 studies were terminated early and all of the post-2015 studies were completed as planned.

I will review the key efficacy findings now. Study 1056 is the 2-dose placebo-controlled study. When these studies were planned, the

three-component composite endpoint of WOMAC pain, WOMAC function, and the Patient Global Assessment was used to support a proposed indication of signs and symptoms of osteoarthritis. Since tanezumab does not affect the signs of osteoarthritis, the current indication is the pain of osteoarthritis, and we're going to focus on the WOMAC pain subscore.

I've included all three primary efficacy endpoints here, although I draw your attention to the first row, WOMAC pain. The study was positive, as shown with the boxed p-values from our analysis. This slide is merely for me to emphasize the treatment effect size of 0.6 on a 0 to 10 scale, and I will return to this finding later in my presentation.

Study 1057 was a 3-injection, 24-week, placebo-controlled study. It was also positive. Again, because we are considering the indication only of pain of OA, the insignificant p-value on the Patient Global Assessment does not affect our regulatory finding.

These are the changes in WOMAC pain versus time curves for Study 1056 and Study 1057. Time in weeks is represented on the X-axis, and the change from baseline WOMAC pain subscale is represented on the Y-axis. Note the scale of 0 to 5, which is half of the full-scale. Nonetheless, the shape of active placebo curves is typical for a positive study. You can see clear separation between placebo and the active groups as early as week 2.

Study 1058 was a 7-dose NSAID-controlled study. As you can see, there was no difference between NSAIDs and tanezumab 2.5 milligrams subQ every 8 weeks, the dose proposed for marketing. The sample sizes were very large for an OA study, so the insignificant p-values were unlikely due to inadequate power.

The prior table reflects the static results at week 16. The slide that I have following this one is the WOMAC pain versus time curve for Study 1058. This diagram is designed to refresh your memory and emphasize the pre-randomization in Study 1058.

Patients had to have been on a stable dose of prescription strength NSAIDs for 30 days prior to screening and report a WOMAC pain of at least 5 out of 10. The actual mean pain scores at screening was approximately 7. Patients were then screened, underwent analgesic washout, and entered an open-label trial of prescription strength NSAIDs, either naproxen, celecoxib, or diclofenac.

Patients had to fail that run-in by reporting a pain score of at least 5 in order to be randomized. Approximately 15 percent of the patients did not meet this criteria, as their pain score had improved on the NSAIDs regimen, and they were therefore not randomized. The mean pain score at randomization was also approximately 7.

Collectively, these pre-randomization activities provide empiric evidence that patients randomized had not responded to open-label NSAIDs. Patients were then randomized to 1 of 2 doses of tanezumab or to remain, or the same NSAID regimen. Dosing post-randomization was double-blind, double-dummy. Patients were dosed with an oral

NSAID, or NSAID placebo daily, and received an active or placebo injection every 8 weeks.

These are the pain curves for Study 1058. I reviewed pre-randomization activities and showed how one-third of the patients stayed on the same regimen. In light of that, the pain curves from Study 1058 are perplexing. Patients who remained on the same NSAID regimen, with the addition of placebo tanezumab, experienced a rapid and sustained drop in pain and never separated from the active arm. This could represent placebo response, although placebo responders typically do not experience treatment over a one-year period.

I will now move on to the last part of my presentation. The applicant has emphasized the clinical significance of the benefit of tanezumab inferred from the clinical trial data. While both placebo-controlled studies clearly support a finding of efficacy, the treatment effect size is 0.5 and 0.6 points out of 10.

For context, data from tanezumab can be compared to other products for osteoarthritis.

While cross-study comparisons can lead to inappropriate conclusions with certain caveats, they may provide limited contextual information. However, I do want to point out that the osteoarthritis populations enrolled in these comparative studies was not restricted to patients for whom the use of other analgesics had been ineffective or not appropriate, and may not have had as advanced disease as the population enrolled in the tanezumab studies.

This table is populated with the treatment effect sizes for several products approved for osteoarthritis. The list is limited to products and studies in which publicly available data include the metric of change in WOMAC pain subscore from baseline, usually to week 12.

The comparative products include an intra-articular steroid, a topical NSAID, and 2 oral NSAIDs. While the treatment effect size versus placebo was not unusual for an osteoarthritis drug, tanezumab does have the lowest treatment effect size of the product whose data are publicly

available.

In the briefing document, the applicant has presented the results of the Health Technology Assessment contracted to Tufts University Medical Center. The authors of that report concluded that tanezumab, NSAIDs, and opioids all result in small-to-moderate improvements in pain and function with few differences between the drug classes.

The authors also concluded that tanezumab demonstrated a safety profile comparable to NSAIDs and opioids, although the report noted serious NSAID-related cardiovascular and gastrointestinal adverse events.

This table summarizes the differences in methodology between what the Tufts and the FDA teams did. This will allow me to illustrate some of the strengths and weaknesses of the Tufts report compared to the review conducted by FDA.

The Tufts group applied current meta-analysis techniques to interventional randomized-controlled trials in patients with osteoarthritis limited to treatment of placebo,

NSAIDs, opioids, and tanezumab. I note that the literature contains no relevant studies of tanezumab versus opioids and only one study of tanezumab versus NSAIDs, which we have reviewed in detail.

The tanezumab FDA team used standard marketing application review techniques and recruited expertise from various consultants within the agency. We have applied the same process that is used for regulatory decision making across CDER. The group from Tufts was limited to summary data at the study level. We reviewed raw subject level data from the ADaM files, adverse event narratives, and source documents.

As a meta-analysis, the Tufts report was subject to heterogeneity in study population and duration, although the data was then pooled for analysis and reporting. We assessed the concurrent control data, subjected it to confirmatory statistical analysis, and conducted a post hoc analysis as needed. While for some pooled analysis, the Tufts authors were able to aggregate

a large number of studies, I want to emphasize that the actual comparisons to tanezumab were limited to just five studies. Everything else is an indirect comparison.

With regard to the key efficacy metrics from which conclusions are drawn, the Tufts team averaged the difference from baseline to end of study in the pain score. While the data from approved products that I showed earlier are also subject to heterogeneity in patient population and study duration, they report the same efficacy metric calculated identically.

For safety, the Tufts team was limited to calculating raw incidences for individual adverse event terms or groups of terms, and they chose to express them as risk difference. In our review, we conducted multiple analysis of the raw safety data to provide a comprehensive assessment, including incidence, normalized for exposure, risk over time, and other analyses that Dr. Pokrovnichka will cover in her presentation.

In conclusion, tanezumab 2.5 milligrams subQ

is superior to placebo for pain and function, but is not superior to prescription-strength NSAIDs, and the treatment effect size is modest. Thank you.

FDA Presentation – Anjelina Pokrovnichka

DR. POKROVNICHKA: Good afternoon. My name is Anjelina Pokrovnichka, and I'm the clinical reviewer in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine, who participated in the review of safety data provided in the tanezumab BLA application. I would also like to recognize the contribution of my colleagues from the Division of Biostatistics VII and the clinical data scientists who provided key statistical support for the review of this application.

The applicant has already presented information regarding osteoarthritis, the science behind tanezumab, the clinical development program, and the top-line findings that they believe are critical for your understanding of tanezumab. Undoubtedly, the panel recognizes that this is a

large and complex application. Thus, I will not reiterate information that has been already conveyed. I will start my presentation by explaining where I focused my attention, then I will take a moment to review areas with which, at this point in our review, our conclusions align with the applicant's conclusions.

Most of my presentation, however, will encompass issues that warrant further consideration. These issues pertain to certain aspects of joint-related adverse effects and fundamental questions about risk management for this product. Last, I will summarize points upon which we have been able to make firm conclusions and questions that we still consider to be open.

The FDA review of joint safety focused on the clinical studies conducted after release of the clinical hold in 2015, referred to as post-2015 studies. I will cover these in detail later in my presentation, but from the perspective of safety, the pre-2015 studies are not comparable to the post-2015 studies because of differences in the

patient selection, dose selection, safety monitoring, and duration of follow-up.

As we conveyed in the background package, our review of tanezumab has been an iterative process. We reviewed summary data, which would lead to another question, which might lead to another, and so on. We believe that there are several critical unanswered questions that I will summarize at the end of my presentation.

As I just described, the post-2015 studies can be clearly separated from the earlier studies. The genesis of this division lies in the 2012 advisory committee meeting. In this meeting, clinical data for tanezumab and other anti-NGF agents were reviewed. I have summarized the key action items from that meeting on this slide.

To mitigate the joint safety risk, sponsors were advised to incorporate stringent safeguards in future studies to determine which patients are at risk for joint destruction and which patients might benefit from anti-NGF therapy and to determine the underlying pathophysiology for the joint adverse

events.

I alluded to this earlier, but I want to reiterate what measures to better define the risk of joint destruction were added to the tanezumab development program at the resumption of the clinical development in 2015.

Important measures included institution of standardized imaging studies of the large joints, use of so-called central reader, a musculoskeletal radiologist, adding of criteria for rapid joint destruction, and stopping drug in patients who met those criteria.

I will move on to summarize the accordant findings. In the BLA submission, the applicant has acknowledged that tanezumab is associated with rapidly progressive osteoarthritis -- acronym, RPOA -- abnormal peripheral sensation, and peripheral edema.

Our review of data confirmed that joint destruction and development of abnormal peripheral sensation are the main safety concerns associated with tanezumab. We reviewed serious adverse

events, adverse events leading to discontinuations, and common treatment-emergent adverse events.

The pattern observed for the major safety events reinforced that joint destruction is the critical finding for this molecule. We note that events of abnormal peripheral sensation are another clear adverse reaction for this compound, however, I will not focus my presentation on the neurologic adverse events because they were largely mild to moderate in intensity and were generally self-limited.

The next portion of my presentation will cover the major topic of joint safety in tanezumab studies. My presentation of the joint safety will emphasize three areas of controversies. The Kaplan-Meier analysis does not show a flattening of risk throughout the treatment period and the trajectory of the incidence of joint safety events with long-term therapy is unknown.

The 2012 advisory committee emphasized the importance to elucidate patients who particularly benefit from this drug class, as well as to

identify patients who are at higher risk for joint events. We have only identified one risk factor for joint destruction. Last, there are no good data to support the conclusion that the proposed REMS will be effective or feasible.

Joint safety events fall into two basic categories, all-cause total joint replacement and findings that did not result in total joint replacement. I will cover the latter first.

As you have seen, rapidly progressive osteoarthritis type 1, RPOA-1, was the most common form of adjudicated joint safety event. I will discuss why we think that RPOA-1 is a significant lesion. I will review data for the metric of composite joint safety events from the three post-2015 studies. Last, I will spend time discussing whether we can predict this adverse reaction and/or mitigate the risk.

It is important to remember that there is no animal model for RPOA. Contrary to the 2012 advisory committee request, there is no accepted pathogenetic mechanism to inform patient selection

or to prophylax this issue. Last, in most cases, the finding was clinically silent. Tanezumab-related joint destruction is largely an insidious process that requires sensitive signal detection.

As you saw in the applicant's presentation, the large majority of the composite joint safety events detected were classified as RPOA-1. Here are the criteria used by the applicant to make a diagnosis of RPOA-1. For context, joint space width in a normal joint is between 4 and 5 millimeters. Thus, RPOA-1 represents loss of about half of the joint space in a short one-year time period.

Given that most patients had advanced disease on imaging, it is important to recognize that, mathematically, this criterion could not be met in some patients. Changes in the joint anatomy for such patients were not captured as neither RPOA-1 nor RPOA-2, and thus remained undetected.

Last, it is not clear whether plain radiographs are adequate to detect this signal.

The applicant added a requirement for an MRI confirmation of x-ray identified RPOA-1 soon after starting the post-2015 studies.

We conducted a literature search screen for normal radiographic progression in joint space width in patients with osteoarthritis. The articles we found showed that the level of deterioration as defined by the applicant indeed signifies a very rapid osteoarthritis progression that is well outside of the natural history of the disease.

Tanezumab is associated with a dose-related imbalance in events included in the composite joint safety endpoint. Here is our risk analysis of the composite joint safety endpoint from pooled post-2015 placebo-controlled studies, Studies 1056 and 1057, in which only 2 to 3 doses of tanezumab were administered.

The risk difference when compared to placebo, 2.4 additional events per 100 patient-years of follow-up for the 2.5-milligram tanezumab dose and 4.6 for the

5-milligram dose. These results suggest that the number needed to harm to observe one additional composite joint safety event on tanezumab 2.5 milligram relative to placebo is 41 patients followed for one year. The take-home messages are, number one, there were no events in the placebo group and, number two, there is a clear dose-response.

We considered Study 1058 to provide the best data to inform the joint safety profile of tanezumab for several reasons. Because tanezumab is intended for chronic use, it is important to understand the risk of joint destruction with longer duration of treatment.

Study 1058 was significantly longer, one year or 7 doses, compared to the 2 or 3 doses placebo-controlled study. The comparator treatment in Study 1058 was a non-steroidal drug, the class of drugs that is most widely used to treat the pain of OA in clinical practice. Also, Study 1058 included a robust imaging surveillance with both x-ray and MRI images obtained at multiple time

points.

As illustrated in this slide, the incidence of the composite joint safety endpoint with tanezumab was also increased in comparison to non-steroidals. The estimated hazard ratio for the 2.5-milligram dose was 2.6, and for the 5 milligram was 5 when compared to prescription strength of naproxen, celecoxib, or diclofenac.

This result suggests that the number needed to harm to observe one additional composite joint safety event on tanezumab 2.5 milligrams, relative to non-steroidals, is 43 patients followed for one year.

Osteoarthritis is a chronic disease, and if tanezumab was approved, most patients would be expected to be treated for years. Thus, because the clinical study data are largely limited to 56 weeks of treatment, we generated and assessed Kaplan-Meier curves to understand the trajectory of incidence of composite joint safety events.

Throughout this presentation, each treatment arm is color-coded. I have also added a vertical

black solid line to indicate the average end of treatment and a black dashed line at the average end of follow-up.

Here are the curves for the pooled placebo-controlled studies. The curves show clear rising incidence throughout the follow-up period. As to be expected, there are very few patients at the right end of the figure, and the interpretation of the curves to the right of the black dashed line is unreliable due to the low numbers.

Here are the Kaplan-Meier curves for the composite joint safety endpoint in the non-steroidal controlled study in which patients received one year of double-blinded treatment and were followed for 6 months after the treatment was discontinued. The figure illustrates that composite joint safety events continue to accumulate over time during the study, with most appreciable separation between treatments after one year, which marks the end of the treatment period.

In this study, scheduled imaging occurred at week 24, week 56, which is the end of treatment,

and week 80, which is the end of the follow-up and also the end of the study, marked with a black dotted, black solid, and black dashed perpendicular line on this figure.

As you can see, there is an upsurge of cases around these scheduled imaging time points. But the big upsurge at week 56, compared to the small upsurge at week 24, suggests that there is a latency for the joint events that requires a longer observation period for their detection. Also, the Kaplan-Meier curves do not suggest that the risk of joint destruction plateaus after one year. The rates and risk of composite joint safety events with continued dosing past one year are unknown.

This slide illustrates the insidiousness of the destructive process, the need for good predictive factors, and the need for tight surveillance. There was a question about the involvement of healthy joints, and the FDA analyses are shown on this slide.

This is a summary table of cases of joint destruction that occurred in joints assigned a

Kellgren-Lawrence grade 0 or 1 at baseline in Study 1058, which is a radiographically normal or nearly normal joint. As you can see, the cases of composite joint safety events occurring in healthy joints are concentrated in patients treated with tanezumab, and the imbalance is clearly dose dependent.

Given that RPOA-1 is mostly asymptomatic, it is important to understand what happens to patients following detection of RPOA-1 and treatment discontinuation. As I showed you in the Kaplan-Meier curves earlier, there is a latency to the development of joint events, and therefore patients who develop an event would have to be followed for a long period of time to assess whether the lesion progresses, stops, or potentially reverses.

Unfortunately, limited data are available to inform this question, shown here. Only about half of the patients who developed RPOA-1 had imaging more than 4 months after the diagnosis was made, and only 13 of those had imaging more than 6 months

out.

I will discuss Study 1025 in greater detail on the next slide, and we agree with the applicant that concomitant non-steroidals and tanezumab therapy is a risk factor for joint safety events. The applicant has asserted more severe OA at baseline, based on Kellgren-Lawrence scoring, portends a higher risk of RPOA. Our analysis did not confirm this. Maximum KL grades of any joint at screening did not predict the risk of composite joint safety events. Tanezumab was associated with increased risk in patients with all KL grades.

We also know that composite joint safety events occurred in healthy joints. The pre-2015 data, specifically Study 1025, showed that the rates of joint safety events were roughly doubled to when tanezumab was co-administered with NSAIDs. Because of the utility of non-steroidals in the management of OA and their availability as non-prescription medications, this drug interaction is considered very important.

The post-2015 studies heavily restricted

non-steroidal use. In the BLA submission, the applicant conducted exploratory analysis to assess whether the small amount of non-steroidal use permitted in these studies affected the incidence of the composite joint safety endpoint.

Pfizer concluded that limited use of no more than 10 days per 8-week dosing interval was not associated with an increased risk of joint safety events. However, because non-steroidal use was not a randomized treatment strategy in the post-2015 studies, we consider this analysis difficult to interpret.

As I described previously, we consider the joint safety events, even the lowest grade of RPOA-1, to be clinically significant lesions. Total joint replacements represent a hard endpoint of obvious clinical significance. While total joint replacement is a definitive treatment for osteoarthritis, the surgical procedure is major and the rehabilitation is arduous.

Thus, standard of care is to postpone total joint replacement as long as possible, and total

joint replacements are performed in the setting of end-stage osteoarthritis. However, numerous factors, including ethnicity, gender, psychosocial considerations, comorbidities, surgical risks and, sadly, insurance status, may influence patients' decision to undergo a joint replacement surgery.

Despite those confounders, tanezumab shows a signal for all-cause total replacement in the post-2015 studies. I will also discuss what is known about outcomes following total joint replacement in the setting of prior tanezumab therapy.

This slide summarizes the risk difference for total joint replacement in Study 1056, a placebo-controlled, 2-dose study. The hazard ratio is 2.1 at a 2.5-milligram dose. A signal for total joint replacement was not observed in Study 1057, the 3-dose placebo-controlled study. The high incidence rate of total joint replacement in the placebo group in this study speaks for fundamental differences in the patient population.

We have assessed why the findings in this study are different. Compared to the other two

post-2015 studies, the patients in 1057 were about five years older, with a higher proportion of subjects in the age group of over 65. They also had more advanced osteoarthritis on baseline imaging. Study 1057 was conducted in Europe and Japan, and both 1056 and 1058 were conducted entirely or partially in the United States.

As I mentioned earlier, the decision to undergo a total joint replacement surgery is influenced by many factors. Differences in the standard of care of how patients are managed in general is one of them and may vary between different countries.

One clinical site in Hungary reported more than half of the total joint replacements in Study 1057. We had planned to inspect this study to better understand criteria for total joint replacement or other explanations. However, due to the COVID-19 pandemic, it has not been feasible to conduct this inspection.

A hazard ratio of 2.1 was seen in Study 1058, the non-steroidal control study. This

study had by far the longest treatment duration adverse event capture period, largest sample size, and global representation of study centers, making it the most suitable to assess the risk of total joint replacement. These results suggest that the number needed to harm to observe one additional total joint replacement on tanezumab 2.5 milligrams, relative to non-steroidals, is 34 patients followed for one year.

This figure illustrates the prior three tables in the form of a bar graph. As you can see, Study 1057 stands apart from the other two studies. We consider the total joint replacement data across the studies to be indicative of the major irony of tanezumab. The drug accelerates the degenerative process of osteoarthritis in some patients, resulting in both composite joint safety endpoint and total joint replacement surgery.

The hazard ratio for total joint replacement for the 2.5-milligram tanezumab dose is approximately 2. Here are the Kaplan-Meier curves for total joint replacement for Study 1056. It

shows clear separation between the treatment groups. It is difficult to extrapolate the shape of these curves beyond one year. No separation between the Kaplan-Meier curves for total joint replacement is appreciable for Study 1057. As I explained, we consider this study to stand apart from the other two studies.

Here is the non-steroidal controlled study. Again, we see clear separation between the treatment groups. In this longer term study, the curves continue to separate throughout the end of the study, and we do not have data to extrapolate what would happen with longer-term dosing or follow-up.

As noted here, the literature reports that total joint replacement surgeries are associated with complex reconstructive efforts and technical difficulties when performed in the setting of significant bone loss, which in turn may compromise the success of the surgery.

This concern was the genesis of Study 1064, which was a prospective observational study that

enrolled patients from Studies 1056, 57, and 58, who had undergone total joint replacement to collect follow-up data. Evaluations included surgeons' assessment of procedural difficulties during surgery, complications after surgery, and any post-surgical additional or corrective procedures that were performed. This study also evaluated patient-reported questionnaires.

One hundred fifty patients were enrolled out of the 258 patients who underwent a total joint replacement. However, a very small number of the 150 patients enrolled in Study 1064 had a total joint replacement associated with a joint safety event, 12 out of the 150, or 8 percent.

The number of patients with total joint replacement due to joint safety events of advanced destruction, like RPOA-2 or osteonecrosis, was even smaller, 9 out of the 150, to allow any meaningful assessment of the impact of bone loss on the outcome of total joint replacement surgery in this patient population. Also, as this was not a randomized study and the management of patients

post-surgery was not standardized, any safety comparisons between treatment groups, based on treatment assignment in parent study, are, at best, exploratory.

The last portion of my presentation will cover prediction and risk mitigation measures. This issue is critical for the reasons I have listed on this slide. The basic science has not yet elucidated the mechanism by which tanezumab accelerates the osteoarthritic process. There's no animal model.

This leaves us with empirical clinical study data by which to infer what patients are at greater risk. We agree with the applicant that concomitant non-steroidal use is a risk factor. However, we do not agree that high Kellgren-Lawrence scores at initiation of treatment necessarily portend a higher likelihood of a joint safety event. We also note that cases of adjudicated joint events have occurred in radiographically healthy joints.

Given the lack of the development of a clinical biomarker, the applicant is limited to

medical imaging for surveillance. The imaging protocol will have to be compromised between cost, feasibility, sensitivity, and specificity. As I will describe later, we do not know whether the risk mitigation scheme proposed will be effective.

In the post-2015 studies, there was protocol-specified imaging surveillance summarized here. Serial plain radiographs were the foundation of the risk management scheme. Imaging studies were assessed by a blinded, highly-trained musculoskeletal radiologist for probable joint safety events. The identified events were then evaluated by an adjudication committee for final classification.

Despite a high degree of standardization and expertise, there was substantial discrepancy between the central radiologist and the adjudication committee. The central reader diagnosed 241 cases of composite joint safety events compared to 145 by the adjudication committee.

This discrepancy is particularly surprising

because the diagnosis and grading of a composite joint safety event is based solely on imaging. It also illustrates the complexity and the uncertainty of the classification process, alluding to the challenges that would be faced in clinical practice. Our review of some cases implies that MRI might be more sensitive and specific in identifying cases of tanezumab-related joint destruction, particularly in the early stages.

Given our lack of understanding about the pathogenesis of these events, the only realistic option is to stop the drug once radiographic changes are evident. However, there are insufficient data to inform what proportion of patients who developed RPOA-1 will go on an accelerated course of total joint replacement.

The existence of the pre-2015 studies presents us with a natural experiment from which we might infer whether the applicant's risk mitigation measures were effective. The pre-2015 studies were designed and conducted prior to the identification of the joint safety signal. Thus, they contained

standard non-specific clinical study risk mitigation measures.

As I have described, following the 2012 advisory committee meeting, substantial risk mitigation measures focused on the joint safety were added across the program. Thus, on face, comparing the incidence rate of composite joint safety events and total joint replacement should inform the effects of the safety measures.

After careful consideration, unfortunately, we think that it is not possible to compare the two sets of data. This table summarizes the confounds for this comparison. In general, the pre-2015 studies used higher doses and included the IV route, which resulted in higher tanezumab exposures. Given that the joint safety risk is dose dependent, this would tend to bias the assessment towards concluding that the risk mitigation measures are effective.

The surveillance for joint events was robust in the post-2015 studies, and the applicant introduced the blinded central and reader

adjudication committee favoring detection of more events. The definition of RPOA-1 changed. The threshold of decreasing joint space width increased from 1 millimeter in pre-2015 to 2 millimeters in post-2015 studies. This change biases against detecting a joint event.

As it was discussed, there is a latency to a joint event, and joint events can occur long after drug discontinuation. The follow-up in the pre-2015 studies was only 8 weeks compared to 24 weeks in the post-2015 studies. This increases the likelihood of detecting a joint event in the post-2015 studies.

As I asserted early in this presentation, the data submitted in this BLA allow us to draw some conclusions with confidence but resulted in other questions. We conclude that tanezumab is associated with a risk of accelerating the degenerative process of osteoarthritis, and tanezumab is associated with generally mild self-limited disturbances in peripheral sensation. The joint events are predominantly clinically

silent, and tanezumab can target healthy joints.

There are several questions left unanswered that I have listed in the right column of this table. Why does tanezumab do this? What patients are most susceptible? Does the risk plateau rise slowly or rise sharply with longer treatment? Does stopping drug after RPOA-1 improve outcome? If not, the proposed risk mitigation measures will be ineffective.

There are scant data on total joint replacement outcomes in the setting of tanezumab therapy. If indeed the bone loss leads to worse outcomes, given the high likelihood that patients will require one or more joint replacements over their lifetime, this could represent an unacceptable level of risk. Thank you for your attention.

(Pause.)

DR. SUAREZ-ALMAZOR: Dr. Ho, please start your presentation.

(No response.)

DR. CHOI: Martin, do you think you're on

mute by any chance? We can't hear you. If you can hear us, can you please start your presentation now?

MR. HO: Hello? Can you hear me now?

DR. CHOI: Yes. Thank you.

FDA Presentation – Martin Ho

MR. HO: Good afternoon. My name is Martin Ho, associate director at the Office of Biostatistics and Epidemiology at the Center for Biologics Evaluation and Research. I am presenting our reviews of the patient preference study of tanezumab on behalf of the Center for Drug Evaluation and Research.

This figure illustrates the overall schematic. Let's start from the blue box on the left. The applicant first conducted a patient preference information study, or PPI study, to elicit preference information.

The PPI study proceeded in two phases. In phase 1, 4 focus groups, each with 6 to 8 participants, were conducted to identify concepts that were related to preferences for treatment of

chronic pain. In phase 2, based on the finding from the focus groups, the applicant specified several attributes and their levels for preference elicitation using two different methods; first, discrete choice experiment, or DCE, and second, best-worst scaling, or BWS.

To elicit preferences, the applicant administered an online survey that comprised prespecified questions using experimental design for the DCE and BWS questions. In addition to the 6 primary treatment attributes included in the DCE questions, the applicant wanted to assess other risk attributes.

To ensure the number of attributes in the DCE questions being within the cognitive feasibility of average respondents, the applicant implemented a separate but related BWS component to assess other risks attributes that could not be captured in the DCE.

Using the elicited preference data from phase 2 as input, the applicant conducted a quantitative benefit-risk analysis using

multi-criteria decision analysis to weigh the benefits and risks of various targeted drugs using clinical data specified by the applicant.

In general, we considered the applicant's PPI study and the subsequent quantitative benefit-risk analysis followed good research practices in their design, conduct, and the analysis. However, during the review of these studies, we identified several issues with the study that rendered the elicited patient preference information and the subsequent quantitative benefit-risk analysis inapplicable for our consideration. The presentation today will focus on the patient preference study, or PPI study, and the issues that we have identified.

First, the main objective of this study was to quantify the patient's preferences for attributes of pharmaceutical treatments for chronic moderate-to-severe pain associated with osteoarthritis, or OA, or chronic lower back pain, or CLBP, that are relevant to patients and differentiates tanezumab from alternative

analgesics.

The applicant quantified the relative importance of each evaluated treatment attribute and estimated the trade-offs that the study participants are willing to make among these attributes. In particular, the applicant looked at the maximum acceptable risk that the study participants are willing to tolerate in exchange for an improvement in a treatment benefit or the treatment frequency.

The applicant has submitted extensive information from the PPI study, however, not all information is relevant for the purpose of this application. First, we only reviewed the result from the United States study. Second, the applicant has submitted results from a mix of respondents who self-reported having OA only, CLBP only, or concurrent OA and CLBP.

Since the indicated a population for this application is OA, the review focuses on the respondents with OA or concurring OA and CLBP. Finally, we only considered five non-monetary based

attributes of benefits, risks, and administration mode and frequency.

For the PPI study, an online survey with DCE and BWS formatted questions were administered to 400 respondents who self-reported or/and self-completed the survey. The DCE questions of the survey comprised 8 choice questions, and an example is shown on the left of the screen. In each question, two hypothetical treatment options were shown, and respondents were required to choose one of them.

The DCE consists of six attributes, and five of them are relevant to this review. First, the benefit attribute is symptom control. The next three attributes concerned risk; additional risk each year of having severe joint problems that require total joint replacement; additional risk each year of having a heart attack; and the risk each year of physical dependence. The last attribute is about administration mode and frequency.

This figure depicts the primary result from

the DCE questions. The X-axis consists of five relevant attributes representing benefits, risks, administration mode and frequency. Each attribute has a set of levels. For example, if you look at the left-most attribute, the symptom control attribute has four 4 levels. They are poor, fair, good, and very good.

The attribute next to the symptom control is incremental treatment-related risk of rapidly progressive severe joint problems requiring total joint replacement. The second level should be 0.5 percent, not 0.2 percent as shown on the screen.

The Y-axis is preference weight and represents the relative importance of the attribute levels to the survey respondents. The greater the preference weight of an attribute level is, the more important or preferred the level is to the respondent. For example, within the attribute of symptom control, the estimated preference weight of a fair state is about zero compared to the poor state preference weight of minus 2.45. This means

that the respondents prefer fair compared to poor symptom control, based on the preference weights.

Based on these results, the applicant concluded in their submitted report that, on average, respondents strongly prefer better symptom control and avoiding the treatment-related risk of physical dependence. Avoiding incremental annual treatment-related risk of heart attack and severely rapidly progressive joint problems requiring total joint replacement were much less important, both statistically and qualitatively, than either improving symptom control or avoiding the risk of physical dependence.

Using the estimated preference weight, the applicant also calculated the maximum risk threshold, or risk tolerance, and concluded that the respondents are willing to accept more than 4 percent additional risk each year of severe joint problems requiring total joint replacement for most levels of symptom control improvement.

That means in exchange for symptom control improvement from poor to fair, or from poor to

good, the respondents were willing to tolerate a 4 percent or above additional risk each year of having severe joint problems that result in a total joint replacement.

We conclude that the evidence submitted by the applicant is insufficient to support their interpretation of the PPI study result that the patients will view severe joint problems as much less important compared to symptom control improvement, and are willing to accept more than 4 percent incremental risk of severe rapidly progressive joint problems requiring total joint replacement. That's because we have identified three key issues. They are inadequate description of severe joint problems requiring total joint replacement; missing critical attributes; and forced-choice format of the DCE question design.

We are the end user of the PPI study result. Unfortunately, we did not have an opportunity to provide at the various critical stage of the study -- to comment on their study design, sample selection and finalization of attributes for DCE.

Our input might have helped to avoid and mitigate some of these issues that we have identified in the review process.

The first issue we identified is missing essential attributes. The main benefit attributes in the DCE were symptom control, and the levels were defined following the Patient Global Assessment for osteoarthritis, or PGA-OA, which was one of the co-primary endpoints used in the clinical trials.

The attributes description in the survey cover a wide range of symptoms, including pain; tenderness; stiffness in the affected joint; loss of flexibility; limitations in the range of motion; grating sensation; and bone spurs that feel like hard lumps. However, based on these attributes in the description, it is challenging to identify the driver behind changes in the attributes. Various combinations of improvement in the list of symptoms could have contributed to the same improvement in the symptom control.

The clinical trial actually has also used

two other co-primary endpoints, the WOMAC pain and functional scores. We cannot discern the respondents in the study, their relative attribution of improvement in overall symptom control, either pain or functional improvement. For example, it is unclear a change in symptom control from poor to fair means the same amount of improvement to patients because the individual patients could attribute it to different combination of changes in pain and function.

Both attributes or co-primary endpoints could have been used in the DCE as we suggested to the applicant in response to our pre-BLA meeting. Unfortunately, the PPI study was completed before the meeting.

In accordance with good research practices, the applicant included the descriptions of each of the attributes in the DCE survey before treatment choice questions. However, in our opinion, the description of the severe joint problems requiring total joint replacement is inadequate.

The box at the bottom contains the verbatim

description in the survey, and the description does not convey the impact and consequences of a total joint replacement on patients' lives; for example, the pain associated with the surgical procedure and the pain and reduction in joint function before, during, and after the rehabilitation period.

At the time of the 2012 advisory committee meeting, the safety events of RPOA and the need for total joint replacement was known. Unfortunately, the moderator guide for the focus group interviews did not include this risk. The guide only focused on efficacy, side effects, risk of addiction, mode of administration, frequency of administration, and out-of-pocket cost. The submitted focus group transcript did not show the moderator following up with participants when they spontaneously brought up the need for total joint replacement or having a prior total joint replacement.

We considered this as a missed opportunity to get the focus groups' input on how they viewed a total joint replacement in terms of their osteoarthritis, especially the potential systematic

risk of tanezumab to their nearly healthy joints as a possible safety endpoint. Had this been done, it would have better informed the descriptions used in the PPI survey. It is unclear if patients completely understand the risk for total joint replacement included in the non-osteoarthritis affected joints.

How much respondents weigh the importance of the risk of total joint replacement depended on their understanding of the risk, potential impact, and consequences on their lives. So therefore, we believe that the inadequate description might have led to an under-weighing of this risk attribute, which in turn led to a high estimated risk tolerance for severe joint problems requiring total joint replacement.

The third issue is regarding the forced-choice format of the DCE questions. The figure on the right is an example of a DCE question with a forced choice. As you can see, respondents are required to choose one of the two options shown in the questions, and they are not allowed to opt

out or choose to stick with their current status quo or current treatment.

The preference weights and maximum acceptable risk estimated using such forced choice from the questions can be different than had the respondents might have chosen to opt out or remain with their status quo. Further, in daily clinical encounters, patients typically select their treatment options in an unforced manner, as they can decline the options presented by their physicians.

So therefore, we believe that the patient preference information should be elicited using a question format that allows for opting out because it reflects a clinical setting outside of the trials.

An additional issue that we have identified is regarding the study sample selection. The participants in the PPI study were members of internet survey panels, and the diagnosis of OA was based on a self-reported diagnosis who identified these respondents with self-reported

moderate-to-severe OA pain, and an online screening tool was used. This tool included questions on worst possible pain in the past week and the pain medications that the respondents are currently using or have ever used in the past two years.

Participants were eligible if their pain score was 5 or greater. However, for those with concurrent OA and CLBP, having 5 or more pain for either condition would have made them eligible. Further, the screening tool required them to self-report that they took or tried three or more classes of pain treatments in the past two years; or two prior classes either excluding NSAIDs or opioids due to contraindications or unwillingness to take opioids; or one prior class of pain treatments excluding NSAIDs and opioids due to contraindications or unwillingness to take opioids.

Unfortunately, no data or evidence was submitted to support the performance of these screening questions. For example, a two-year recall period might be inadequate to correctly identify the respondents' past use of pain

medication. Moreover, the FDA released a patient focused drug development guidance document last year on collecting comprehensive and representative inputs, which discusses the limitations of Web panels.

To sum up, after reviewing the submitted materials, it is concluded that the submitted PPI results were inapplicable to inform our benefit-risk assessment of this BLA for three major reasons.

First, the inadequate explanation of the impact of severe joint problems requiring total joint replacement might have led respondents to underweigh their risk attributes and bias the maximum acceptable risk estimates. Second, the missing pain and function as individual attributes in the preference study may lead to ambiguous interpretation of the benefit in symptom control to respondents. And finally, the survey instrument's forced-choice format may have yielded the wrong type of patient preference information data for regulatory consideration. Thank you.

FDA Presentation – Somya Dunn

DR. S. DUNN: Good afternoon, everybody. My name is Somya Dunn, and I work in the Division of Risk Management. Today, I'm going to present a background on risk evaluation and mitigation strategies or REMS. I will review the applicant's proposed REMS, and then I will present the agency's review of the proposed REMS.

A REMS is a drug safety program that can be required by the FDA for certain drugs. A REMS is designed to mitigate serious risks associated with a drug and includes strategies beyond labeling to ensure the benefits outweigh the risks of the drug.

The FDA Amendments Act of 2007 gave the FDA authorization to require applicants and application holders to develop and comply with REMS programs if it is determined necessary. The FDA has the authority to require a REMS pre- or post-approval. If the FDA determines a REMS is necessary, the REMS components can include a medication guide or patient package insert; a communication plan for healthcare providers; certain packaging and safe

disposal technologies for drugs that pose a serious risk of abuse or overdose; elements to assure safe use, which may restrict distribution; and an implementation system. REMS must include a timetable for submission of assessments.

If elements to assure safe use are determined as a necessary component of a REMS, the elements to assure safe use, or ETASU, can include the following: certification and/or specialized training of the healthcare providers who prescribe the drug; certification of pharmacies, practitioners, or healthcare settings that dispense the drug; limited settings for dispensing or administration of the drug such as a hospital setting; having each patient using the drug be subjected to certain monitoring; the drug is dispensed or administered only with evidence of safe-use conditions, for example, a pregnancy test; or there is enrollment of treated patients in a registry.

These elements may be used in combination to create a specific risk mitigation program.

Additionally, elements to assure safe use must align with the specific serious risks listed in the labeling. They cannot be unduly burdensome on patient access and should minimize burden on the healthcare system, considering, in particular, patients with serious life-threatening diseases and patients who have difficulty accessing health care.

The applicant has amended their REMS proposal from what we placed in the FDA background to include prescriber certification. Their goal is to mitigate the increased risk of rapidly progressive osteoarthritis, or RPOA, with tanezumab by ensuring healthcare providers are educated about the increased risk of RPOA; ensuring that healthcare providers are educated on the documentation of baseline and annual x-rays; and the requirement to submit the patient enrollment form and patient continuation form. They must also counsel patients on the increased risk of RPOA and the importance of avoiding non-steroidal anti-inflammatory drugs, or NSAIDs, while on treatment and for 16 weeks after treatment.

The REMS goal also includes to ensure that healthcare providers are educated on safe use by administering tanezumab only to enroll patients in certified healthcare settings after verification of baseline and annual x-rays and after counseling them on the importance of avoiding NSAIDs. Providers must also be sure that patients are informed about the increased risk of RPOA, the requirement for x-rays at baseline and annually, and the importance of avoiding NSAIDs.

The applicant selected the following REMS elements: prescriber certification; healthcare setting certification; pharmacy certification; patients are enrolled in the REMS and informed of the risk of RPOA; patients must be monitored for signs of RPOA with x-rays and for symptoms of RPOA such as increased pain and/or swelling; and there must be documentation of the bilateral x-rays of the knees and hips at baseline, and yearly thereafter.

In the post-2015 trials, there were patient selection and pre-treatment risk mitigation methods

in place. All patients had baseline x-rays of knees, hips, and shoulders which were read by specially trained radiologists. There were exclusion criteria of other types of pre-existing joint disease and inclusion criteria of patients with more severe osteoarthritis that was unresponsive to or intolerant of multiple standard of care analgesics.

The risk of RPOA is dose related. If approved, tanezumab would be approved for 2.5 milligrams, the lowest dose studied. The applicant's REMS would require baseline x-rays of knees and hips and education of prescribers to exclude patients with other types of pre-existing joint disease, and to reserve tanezumab for patients with more severe or unresponsive osteoarthritis.

The agency is concerned because even with careful selection criteria for patients to begin tanezumab treatment, RPOA can occur in healthy joints. Also, REMS authority allow for prescriber education to be required but cannot require

education of radiologists. Therefore, specially trained radiologists through the REMS is not feasible and raises concerns about the ability to detect RPOA in a real-world setting.

The risk is difficult to identify. There would be variability in the readers of the x-rays, and x-ray interpretations may differ from patient positioning. There were substantial disagreements between experts during clinical trials.

During the post-2015 trials, x-rays of knees, hips, and shoulders were read by specially trained radiologists. Also, NSAID use was limited in these trials. Patients were evaluated for new symptom onset, and tanezumab was stopped if they were not responding.

The applicant proposes that the REMS require yearly x-rays of knees and hips. There is also a requirement for providers to counsel patients not to use NSAIDs and for them to report new symptoms. The REMS would also require educating prescribers to discontinue tanezumab after 2 doses if patients are not responding.

The proposed REMS can support that x-rays are done at defined intervals. However, as mentioned, the REMS cannot require that radiologists be specially trained. Once the x-rays are completed, as we also mentioned in the previous slide, RPOA is not easily identified and followed with x-rays. The changes may be subtle, the readings have subjectivity to them in terms of positioning, and there may be different interpretation. Patients will be counseled not to use NSAIDs and to report symptoms. However, patients may be asymptomatic, and NSAID use may still occur.

If RPOA was identified in a patient during the clinical trials, tanezumab was stopped. This guidance would be provided to prescribers in the REMS. However, we remain concerned about this intervention because the destruction is already underway and irreversible once it is detected. In addition, we don't know if stopping tanezumab will halt further destruction to the joint. Overall, the effects of long-term progression of joint

destruction is unknown.

I wanted to revisit this Kaplan-Meier curve that Dr. Pokrovnichka, our safety clinical reviewer, shared with you earlier. This curve from Study 1058 demonstrates the clear separation between the treatment groups. In this longer term study, the curves continue to separate through the end of the study, and we do not have data to extrapolate what would happen with longer term dosing or follow-up. This raises uncertainties about the ability of the proposed risk mitigation strategies to manage the risk.

In conclusion, the proposed REMS would be a restricted distribution program. In addition to the certifications, there would be a requirement to document that x-rays were performed a pre-defined intervals. The agency would be able to ensure that education is provided for prescribers, pharmacies, and healthcare settings. Patients would be counseled about the risks, and as mentioned, x-rays would be done at required intervals.

However, the REMS cannot reproduce the

strategies that were applied in the post-2015 clinical trial, and the measures that are required are not necessarily going to identify and impact the progression of RPOA. The REMS cannot prevent RPOA from occurring.

Given the modest clinical benefit of tanezumab described by Dr. O'Donnell in her efficacy presentation, we have significant concerns that a REMS would not be able to ensure that the clinical benefit of tanezumab outweighs the risk of RPOA. Thank you.

FDA Presentation – Robert Shibuya

DR. SHIBUYA: Good afternoon. My name is Rob Shibuya. I'm a medical officer in DAAP, and I'm serving as the cross-discipline team leader, we abbreviated as CDTL, for the tanezumab BLA. Since we started this morning, between the applicant and FDA, 10 presentations on tanezumab are complete, and I thank you for your attention. I want to take a couple of minutes now to consolidate and summarize the agency findings.

The applicant has shown substantial evidence

of efficacy versus placebo, although we consider the treatment effect size to be modest. When we use the word "modest," we use the word "modest" based on our comparison to studies that use the same experimental design and validated endpoints. While imperfect, this has been the way the division has traditionally placed analgesic effect size into context.

As Dr. O'Donnell noted, unlike the approved products, the patients enrolled in the tanezumab studies had generally failed or wouldn't use acetaminophen NSAIDs and opioids, which does limit the value of the comparison to other OA products. The other metrics presented by the applicant to provide context also have their own strengths and weaknesses.

Tanezumab carries the risk of joint destruction. Because cases of joint destruction in TJR continue to rise after one year of treatment, we consider the trajectory of this risk when extrapolated to years of therapy to be uncertain. Whether or not patients can appreciate the fact

that tanezumab can damage healthy joints is unknown.

Unfortunately, effective risk mitigations to prevent tanezumab-related joint destruction are few. Minimizing concurrent regular NSAID use may be feasible, and labeling could limit the dose of tanezumab. The applicant has not been able to identify early signs and symptoms of tanezumab-associated arthropathy and has not been able to elucidate the mechanism for this adverse reaction.

The applicant has proposed a REMS with active imaging surveillance. The initial scheme required accurate measurement of joint space width, which showed poor concordance in clinical trials and is likely unfeasible in the real world.

The proposal now is to use Kellgren-Lawrence grade change to guide when to stop treatment. We have not had the opportunity to discuss this internally, however, on face, given how the KL grades are written, I would be concerned about subjectivity and consistency, particularly when

this is applied by community radiologists.

Regardless of the accuracy and precision of an imaging-based, decision-making process, it remains unclear whether the risk mitigation measures used in the post-2015 studies protected patients from bad outcome.

Last, our patient preference information team has explained why the patient preference study was not suitable to inform regulatory decision making. Our team is now ready to take questions from the panel. Thank you.

Clarifying Questions

DR. SUAREZ-ALMAZOR: We will now take clarifying questions for FDA. Please use the raised-hand icon to indicate that you have a question, and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

We have limited time, so in order to give everyone a chance to ask their questions, we would appreciate it if you could be cognizant of time constraints, possibly ask a single question, and we will go around again if time permits.

Dr. Meisel?

DR. MEISEL: Thank you. Steve Meisel from Minneapolis. I want to go back to the question of the effect of this drug on healthy joints. Two of us asked a question of the sponsor early this morning and were given data to show that it did not have any significant impact in terms of RPOA on healthy joints. But the agency believes otherwise, and showed us data to contradict that.

I'm wondering if we can get a little bit more clarity from the agency and/or the sponsor about that particular point, because that's going

to form an awful lot of our conversation tomorrow.

DR. SHIBUYA: We have a slide on this.

Dr. Pokrovnichka, if you could let the Adobe people know what slide to pull up from your presentation. I can start describing.

Of course, there are two --

DR. SUAREZ-ALMAZOR: Please --

DR. SHIBUYA: -- sorry. This is Rob Shibuya. I'm the CDTL.

There are two AEs of interest. There's what we call the CJSE, the confirmed joint safety composite, joint safety event, and then there's total joint replacement, and I'll describe the data for the CJSE first.

DR. POKROVNICHKA: Slide 17, please.

DR. SHIBUYA: Thank you, Dr. P.

In Study 1056, there were no cases. That was the shorter study; 2 doses of drug. In Study 1057, there were a total of 4 cases, 2 of CJSE. All four of them were in tanezumab-treated patients. Two were at the 2-and-a-half milligram dose and 2 were at the 5-milligram dose. Then in

Study 1058, the year-long study -- I think it was slide 77, please.

DR. POKROVNICHKA: Slide 17 --

DR. SHIBUYA: Oh, it's 17.

DR. POKROVNICHKA: -- not 7.

DR. SHIBUYA: So you can see here in 1058, there were a total of 8 cases at 2-and-a-half milligrams. Most of them were RPOA-1.

Does that answer the question?

DR. MEISEL: It does from where you're coming from. There was a discrepancy between this presentation and the sponsor's presentation. To me, it's striking, and maybe later we can have a chance to have the sponsor respond to this. If there's time later, I'd appreciate that; otherwise, that does. Thank you.

DR. SHIBUYA: Okay.

DR. SUAREZ-ALMAZOR: Dr. Richards?

DR. RICHARDS: John Richards.

Dr. Pokrovnichka, they mentioned that they didn't really identify any risks for the RPOA, but they rarely looked at characteristics of the

osteoarthritis. Were there any comorbidities that may have been associated with the progression of joint destruction?

Also, in terms of the neuropathy, there didn't seem to be any risk associated with that. It seemed to be short term. But in a drug that's proposed for long-term therapy, could there be effects of that, that we just haven't seen with the short-term use of the drug that was presented today? Thank you.

DR. ROCA: Hi. This is Dr. Roca; just a quick comment. In order to keep things moving, what I'm going to ask is for Dr. Shibuya to start addressing the question. And if you need additional help from the review team, you can ask Dr. P or Dr. O for additional details.

So I'm going to turn an ask Dr. Shibuya to start addressing your question.

DR. SHIBUYA: Yes. Rob Shibuya, the CDTL. The second one I caught. I'm trying to write them down. The second one I caught, which is the peripheral neuropathy adverse reaction.

My best recollection of this is that they were mild to moderate, and once you stop taking drug, for the most part, they resolved. Obviously, carpal tunnel, I don't recall whether or not any of those required a release. I don't remember any sort of increase in the incidence or severity with the longer study. We have the long study, 1058. The patterns looked about the same between the short studies and the long studies.

Does that answer your question?

DR. RICHARDS: Okay. Yes. Thank you. What I was alluding to was that this drug is proposed to be used for years. Could there be long-term effects that weren't picked up in that long-term study?

The first question was did they look at any comorbidities that could have affected the RPOA? Data presented seemed to focus on characteristics of osteoarthritis.

DR. SHIBUYA: We looked at standard baseline characteristics, but we did not go to the granularity of really looking at specific comorbid

conditions. The applicant might have that level of granularity in their subgroup analyses, but we did not go to that level.

DR. RICHARDS: Okay. I was thinking specifically of things like diabetes or other things that could cause neuropathy; that there was radiculopathy from low-back pain. Thank you. That was all.

DR. SHIBUYA: Yes. We didn't look to that level of detail.

DR. RICHARDS: Thank you. That's all.

DR. SUAREZ-ALMAZOR: Dr. Pisetsky?

DR. PISETSKY: This is in terms of the safety issue and that adjunctive therapy would be possible with this agent. Since it's likely that many of the people will not get a full response -- as the data indicated, a limited number who got a pain level less than 3 -- it's not unlikely that some other agent would -- what would your judgment be about what would be possible?

Would selective joint injections be permitted, topical NSAIDs, analgesics? Because if

the problem is really the extent of analgesia that's leading to the progressive joint disease, anything that would decrease joint pain would be a problem.

DR. SHIBUYA: I'm sorry. I didn't quite understand the question.

DR. PISETSKY: The question is that it's not unlikely that adjunctive therapy will be needed if the effect of the agent is no more than non-steroidal in terms of the extent of pain relief. So it's not uncommon that adjunctive therapy is used in people with osteoarthritis, particularly selective joint injections.

Do you think they would be precluded on the safety plan? And if they are, what else could be done for patient relief?

DR. SHIBUYA: Well, I think the assumption we've been operating under is that these patients that would be eligible for tanezumab would really have sort of reached the end of the road. And the way that we have been approaching it is they're largely looking at opioids, versus tanezumab,

versus joint replacement.

Your question is a good one. We haven't gotten that far in our deliberations about exactly how we would handle concomitant therapies. Most of those concomitant therapies were not allowed in the studies. I think it's a great question that you're bringing up that we haven't considered because other analgesics were largely prohibited in these studies.

DR. PISETSKY: Thank you for that. I just have a related question.

If you look at the number of total joint replacements, while knee is more common than hip, the difference is not that great. On the other hand, in this patient population, the vast majority of the people had knee arthritis.

Is there any explanation of why there was that discrepancy?

DR. SHIBUYA: I'm not aware of -- we haven't done any analyses that would inform that. The knee was much more commonly the index joint --

DR. PISETSKY: Right.

DR. SHIBUYA: -- but we did not specifically look for why there were more events in the knees than the hips.

DR. PISETSKY: No. Just in terms of patient involvement, it was like 85 percent were with knee versus 15 percent with hip. Yet, if you look at total joint replacement, the difference is not as great. So why were the knees much more likely to be the index joint?

DR. SHIBUYA: We haven't looked at that.

DR. PISETSKY: Thank you. That answers my question.

DR. SUAREZ-ALMAZOR: Dr. Cheng?

DR. CHENG: Thank you; a simple question. It seems to me that the REMS program tracks but does not mitigate the RPOA or any of the composite joint safety events that were described, and all of them are clearly irreversible. It doesn't take a study to show that.

Therefore, it seems to me that the proposed REMS program is more accurately a postmarket surveillance program rather than a risk mitigation

program. And I'm wondering is that true or not?

DR. SHIBUYA: As I think we've conveyed in our presentation and in the background document, we have struggled with what this proposed REMS program would actually accomplish. So I think you share the same concern that we do.

DR. CHENG: Thank you.

DR. SUAREZ-ALMAZOR: Dr. Singh?

DR. SINGH: Jasvinder Singh, University of Alabama at Birmingham. I have two questions. The first, was there ever a reliability or inter-rater reliability study done for these lesions, the reading of these lesions. Based on slide 32 by Dr. Pokrovnichka, the numbers were 241 versus 145.

Was such a study undertaken at any time, either prior to post-2015 larger studies or as a part of any study? That's question 1. And I'll hold my second question. It's a little different.

DR. SHIBUYA: Sure. You're talking about the consistency of the central reads, and as far as I know, these were fellowship-trained, musculoskeletal, board-certified radiologists who

got additional training. Pfizer may be able to speak to this more. I'm not aware that there were ever any intra- and inter-radiologist studies done, as far as I know.

With regard to the 241 versus 145, we're confused as well, because when you look at the definition for the different CJSE categories, they really are based upon imaging. What Pfizer has said is that the adjudication committee, which was the smaller number of 145, took into account things like the pain scores. There was some other information available to them, but it really to us is a radiographic diagnosis. We don't understand either the difference between the 241 and the 145. You might ask them.

DR. SINGH: Okay. I just had a quick second question, which is that I think the data that the sponsor has shown, and you've shown us, clearly points to the fact that the number of events -- even pooling data from these post-2015 studies has very few events of CJSE and even TKA, and perhaps longer, larger data would inform this

risk better.

But knowing that that data does not exist, a 4-year study of 4,000 patients does not exist at present, and we know that the mechanism of this medication may be blocking the nerve growth factor, and neurogenic information blockade or blockade of nerve signals, one can almost imagine that the peripheral edema, the neuropathies, which are mild and limited, to RPOA-1 and 2, which is the second moderate severity of neuropathy to TKA, would serve as a spectrum of neurotoxicity, where it might increase the numbers.

Was there an attempt by the sponsor or by the FDA to combine these three groups of adverse events into three potential severities, mild being peripheral edema/neuropathy; moderate being RPOA; and severe being RPOA-2 plus TKA? Was such an analysis thought of or undertaken? Thank you.

DR. SHIBUYA: No. I think it's a great idea that you're bringing the outcomes raised or help put all of them together. We have not done that. We have asked Pfizer. Pfizer has done quite a bit

of work to try to understand the pathophysiology of the joint adverse events. I think we understand theoretically what's going on with the peripheral nerve.

I don't think I'm answering your question. As far as I know, none of us, neither Pfizer nor we, have tried to consolidate all three types of adverse reactions under one mechanism, but Pfizer might be able to answer that question.

DR. SINGH: Thank you. That concludes my questions. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Horton?

(No response.)

DR. SUAREZ-ALMAZOR: Dr. Horton, do you have a question?

(No response.)

DR. SUAREZ-ALMAZOR: You're muted.

Okay. Dr. Honczarenko?

DR. HONCZARENKO: Thank you. Marek Honczarenko, GSK. I have a question. I would like to hear your interpretation of comparison slide 25 of studies 56, 57, and 58.

Essentially, the major difference is related to a higher response or the number of joint replacements in placebo group, in 57. But also what is interesting in this slide is that there is essentially no difference between higher and lower dose across all of the studies, which higher dose is pretty consistent in terms of the readout.

How do you think that this could inform the REMS or potential design of the follow-up studies to ensure the safety, or is it actually reassuring that the higher dose is not that different than the lower dose, which is proposed for approval?

DR. SHIBUYA: Am I showing you the right slide?

DR. HONCZARENKO: Yes.

DR. SHIBUYA: I see dose response for Studies 1056 and 1058.

DR. HONCZARENKO: What I mean is that there is a difference in placebo response between 56 and 57, but when you look at the higher dose, it is essentially consistent. It looks like the effect hits a plateau consistently across three programs.

DR. SHIBUYA: So you're comparing the height of the 5-milligram dose across all three studies. The way I tend to look at it is the concurrent control from each study. I think the way we're interpreting it is, 1056, there's a greater incidence of the events. It's dose related for tanezumab, and it's higher than the control, which would be placebo. Then 1058, it's the same thing. The NSAID has the lowest incidence, and there's dose response. And 1057, as Dr. Pokrovnichka pointed out, is the outlier. We have various reasons why we think that it might be the outlier.

DR. HONCZARENKO: Just a quick follow-up question. We use this parameter as an incidence rate for a hundred patient-years, and isn't it a normalizing factor, independent of placebo to some extent?

DR. SHIBUYA: I'm sorry about the delay. I'm asking the team if anybody -- because I don't think I'm understanding your question correctly. I think Dr. Pokrovnichka might be able to respond.

DR. POKROVNICHKA: Yes. Hello? Hi. This

is Dr. Pokrovnichka. Can you hear me?

DR. SUAREZ-ALMAZOR: Yes.

DR. POKROVNICHKA: Rob, if you can pull slide 77.

I would like to say that given the high incidence of composite joint safety events in 1057, in the placebo group, speaks for fundamental differences in the patient population in these studies.

Sponsor presented baseline characteristics for the pooled 1056 and 1057, we struggled to understand why 1057 was different in terms of total joint replacement outcome. This slide shows that people in 1057 were older. They were five years older and had more advanced KL grade at baseline.

So I think that this may be a potential explanation, that when you get to this point of advanced osteoarthritis, and when you are in the age group of over 65, no matter what medication you're going to be treated with, the total joint replacement awaits you around the corner.

DR. HONCZARENKO: Thank you. That is a

great answer. I appreciate this. Thank you.

DR. POKROVNICHKA: You're welcome.

DR. SUAREZ-ALMAZOR: Dr. Horton?

DR. HORTON: Yes. Can you hear me?

DR. SUAREZ-ALMAZOR: Yes.

DR. HORTON: Can you hear me? Hello?

DR. SUAREZ-ALMAZOR: Yes.

DR. HORTON: Okay. This is Dan Horton from Rutgers. I had a question about the REMS program, and specifically around certification and what was noted to be restricted distribution.

Is that restricted distribution restricted to patients that need the target population for this indication? That is, is it restricted to patients with OA that meet the specifications or would it allow for use outside of POA indication?

DR. S. DUNN: Hi. This is Somya Dunn from the Division of Risk Management. The patient population guidance would be given through the REMS program to the prescribers through the prescriber training. That is guidance, and it would be up to the prescriber to appropriately determine who

should be on the medication. It's an educational process.

The restricted distribution is through the certifications. As you mentioned, we would make sure that the prescriber was educated and then certified. We make sure that the healthcare setting is certified. We make sure that the pharmacy is certified so that when the patient comes in to get the medication or that medication is about to be dispensed, there is a closed loop there, and every checkpoint has been made, and all the certifications have taken place.

But in terms of the patient population and the education, those are things that these settings and the prescriber will attest that they will do, and there are things they'll be educated on. There's nothing to specifically regulate the patient population. I hope that answers your question.

DR. HORTON: Yes, absolutely. The follow-up is, anticipating patients who had entered the program but not necessarily be the intended target

population, does that affect the function or the feasibility of the REMS program in terms of the counseling or monitoring?

DR. S. DUNN: Right. The REMS program is theoretically supposed to operate in the same manner for every patient, and the education that would be going from the prescriber to the patient should be in place with every patient. They'll be attesting that they're informed of these risks and signing, and then when they continue, they would also be attesting and signing, and the x-rays would be done.

So there's going to be no checkpoint to say the patient has osteoarthritis at this level or anything like that.

DR. HORTON: Thank you.

One more question on a different topic, which is the MRI.

DR. SUAREZ-ALMAZOR: Okay. Dr. Horton, I would like to move on because there are a couple of people that need questions also, if you don't mind. We have to absolutely finish by 3:25 I've been

told, but maybe we'll have time to ask questions tomorrow before we start the discussion.

So we only have five minutes, so we can only take two more questions.

Mr. O'Brien?

MR. O'BRIEN: Yes. Thank you. Joe O'Brien, National Scoliosis Foundation. I just wanted to clarify, Dr. Pokrovnichka -- forgive me for her name -- she was just clarifying and answering a question. I want to make sure I understood it.

When we look on slide 22 and 23, looking at 1056 and 1057, I was curious about the fact that previously, the sponsor had showed us that there were 22 placebo patients who in fact had increased, and they were all considered to be natural progression; none of them being rapid progression. And in these slides, we see that in fact, though, there were 25 patients who had total joint replacement.

So I don't understand why there's more than that, but beyond not understanding that, the statement that was made was that once you get to a

certain point -- and the explanation was that these are older patients with a higher KL grade, and it led to my question in terms of what's the natural progression.

What is the natural progression of a KL 3 or 4 of a 65 year old? What will we expect for a total joint placement?

DR. SHIBUYA: Rob Shibuya, the CDTL. We did a literature search, it was some months ago, trying to answer the exact same question. We didn't find anything particularly useful, but I did want to share one publication that was published in, I think, December of last year.

Dr. Pokrovnichka, if you can let me know the backup slide number. It was actually published by our colleagues in rheumatology. They used the osteoarthritis initiative data. The purpose of the study was actually to come up with the best endpoints for the disease-modifying OA drugs. Those lie in the rheumatology division. But what they found is that in doing that, they reported what the -- I'm trying to remember the exact – oh,

that's great. You're bringing it up.

What is important for us out of this paper was the incidence rate of TKR surgery was 2.4 cases per hundred person-years. I think, though, the OAI data is sort of garden-variety, all-comer OA patients. But this is at least one estimate of how many cases you have per hundred patient-years in an average population of patients with OA. That was the only contextual data that we were able to find.

MR. O'BRIEN: Okay. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Thank you very much. We will take a 10-minute break now. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. So we will reconvene at 3:40 p.m. Eastern time.

(Whereupon, at 3:23 p.m., a recess was taken.)

Open Public Hearing

DR. SUAREZ-ALMAZOR: We will now begin the open public hearing session.

Both the FDA and the public believe in a

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the 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 your participation in the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

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

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself. Please state your name and any organization you're representing for the record.

DR. SEYMOUR: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Meg Seymour, a senior fellow at the center. We analyze scientific data to provide objective health information to

patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

A major question is whether tanezumab is safe and effective to treat moderate-to-severe osteoarthritis when other treatments are ineffective or inappropriate. Unfortunately, there's no convincing evidence that this drug is more effective than NSAIDs, and there are no data directly comparing its risk or benefit to opioids. However, there are serious risks, even after patients discontinue use. We agree with FDA scientists that this drug safety profile is not comparable to NSAIDs or opioids.

Let's look at the data on rapidly progressing osteoarthritis. The severity was categorized into two groups, RPOA-1 and RPOA-2. RPOA-1 was 2 to 4 times higher in patients treated with the drug compared to patients treated with NSAIDs. Worse yet, 15 percent of those who developed RPOA-1 and 60 percent of those who

developed RPOA-2 ended up needing total joint replacement surgery. In fact, patients taking this drug were 2 to 3 times as likely to need joint replacement as patients taking NSAIDs.

This should be unacceptable, especially since there is also evidence that joints may continue to deteriorate even after the drug is discontinued, and that RPOA can occur in joints that were healthy prior to treatment with the drug.

You are asked whether the proposed REMS protocol will ensure that the benefits outweigh the risks. We agree with the FDA assessment that the proposed REMS measures are not feasible and that there are no clinical data to support them.

Do you think these mitigation strategies would be replicated in most clinical practices? I respectfully ask you to consider how real-world use of the drug would affect patient outcomes if the drug was approved. For example, several studies excluded patients at risk of cardiovascular events such as those with cardiovascular disease. Since both joint pain and CBD are associated with being

overweight, how realistic is it to assume that this drug would not be prescribed to patients with cardiovascular risks?

Also, is it realistic to assume that patients will not use this drug while also taking NSAIDs, which would double or triple the risk of joints being severely damaged by RPOA.

Another shortcoming of the data is the lack of information about safety when used for more than one year. Pain medication for osteoarthritis tends to be taken for years, not months. The bottom line is we agree with the FDA's assessment that the risk mitigation measures proposed are not likely to be feasible or effective.

When you vote tomorrow, we urge you to focus on the lack of proven safety and effectiveness in the clinical trials, as well as higher risks when used in the real world. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 2, your audio is connected. Please begin and introduce yourself. State your name and organization you're representing for the

record.

DR. AMASHA: Yes. My name is Raimy Amasha, and I'm a physician in Austin, Texas in private practice. I'm not representing an organization, and I have no financial support or sponsor in the process of this presentation.

Good afternoon. I am, as I said, a physician in Austin, Texas who has been in private practice since 2013 after completing my interventional pain management fellowship at the Johns Hopkins Hospital, and I'm medical director of compliance in my practice.

Osteoarthritis is a common problem that clinicians address daily, and it affects people of all ages, gender, race and socioeconomic status. Each day, I see patients in the clinic who struggle with severe osteoarthritis, but their circumstances are very different.

"Doctor, I do not want surgery unless I absolutely have to. Please let me know if you hear of any new treatments available," is a typical sentiment shared in the exam room; yet, other

sentiments echo our hallways, too. "My surgeon told me I'm not a surgical candidate. What do I do now; live the rest of my life in pain?" Or "I work from morning to night daily to put food on the table. I simply cannot be out of work to have surgery. I need help to function."

Each sentiment reflects a person who is confronted with pain and the limitation of function due to severe osteoarthritis, grappling with what therapeutic options are best for their own circumstance. As diverse as people's circumstances are with pain control and function, are there individual preferences for therapeutic care and their comorbid conditions? Consider these scenarios for severe knee osteoarthritis.

A 74-year-old male with a history of stroke and coronary artery bypass has a sensitivity to opioids and cannot take any oral NSAIDs. Knee injections only offer two months of quality relief; or a 54-year-old, peri-menopausal female with a GI ulceration history does not want any pills and prefers interventional steroid injections, but has

a family history of osteoporosis. Hyaluronic acid injections just don't work as well.

A 42 year old male is not at all interested in injections, has tried acetaminophen, NSAIDs, and two stints of physical therapy. He's requesting short-acting opioids for severe pain when he lays awake at night and cannot take it.

Each of these scenarios reflect people in our communities and our clinics that healthcare workers see on a daily basis. It is apparent how diverse patient circumstances, preferences, and comorbidities can be. Thus so, too, must be the treatments available to them.

What years in the clinic have brought to light is that there is no perfect treatment. Rather, best care is delivered by carrying appropriate patient selection to available treatment modalities for benefit maximization and risk mitigation. But we should not be complacent that all we have to offer these patients are the treatments already before us.

For many Americans, the ability to keep

moving is integral to their mental health, as well as their physical health. A popular saying when describing societies' hopefulness of aging activity level is 40 is the new 30 or 60 is the new 50. It is a hopeful reminder that as we age, quality of life doesn't have to reduce to immobility. That optimism is a direct result of pushing the frontier of what is possible in medicine safely through the marriage of careful science and responsible clinical practice.

On the frontlines in the healthcare field and volunteering with awesome public health to give code [ph] vaccine, I have seen, firsthand, the miracle of what science and technology and medicine can do in the hands of motivated healthcare workers. I'm here before you today equally excited to see what advancements in medicine holds for osteoarthritis, and I can tell you our patients and our communities are, too. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 3, your audio is connected. Please begin and introduce yourself. Please state

your name and any organization you're representing for the record.

DR. CAROME: Good afternoon. I am Dr. Michael Carome, director of Public Citizen's Health Research Group. I have no financial conflict of interest.

Public Citizen strongly opposes approval of tanezumab because the three phase 3 clinical trials that tested the drug in the intended target, the osteoarthritis patient population, demonstrated that it fails to provide clinically meaningful benefit compared with either placebo or NSAIDs, but does dramatically increase the rates of rapidly progressive osteoarthritis and total joint replacements in a dose- and duration-dependent manner. As a result, the risks of the drug far outweigh its benefits. Public Citizen's March 10th comments, submitted to the docket for this meeting, provide more detail on our views.

Regarding safety, we note the following. Tanezumab causes accelerated joint damage after as low as two 2.5-milligram doses. Studies 1056, 57,

and 58 demonstrated that tanezumab causes a dramatic, statistically significant, and clinically important increase in the rate of RPOA and total joint replacements in a dose- and duration-dependent manner.

Despite the robust risk mitigation strategies employed in all three trials, that were intended to minimize the risk of adverse serious joint events, an unacceptably high number of such events still occurred. In a real-world setting, where there would not be the same rigorous screening and monitoring of patients, the incidence of such serious adverse joint events almost certainly would be significantly higher.

Per the FDA, there is, quote, "evidence that tanezumab can target healthy joints." Of the 33 composite joint safety endpoint events that occurred in joints with baseline radiographically healthy joints, 31 were in tanezumab-treated patients and only 2 in the naproxen-treated patients The proposed REMS is not sufficient to mitigate the risk of RPOA and does not ensure that

the benefits of tanezumab outweigh the risks of RPOA.

As the FDA noted, quote, "Stopping tanezumab after patients developed RPOA-2 does not appear to be effective in preventing further damage to the joints. In addition, the required precision and consistency of the medical imaging and interpretation do not appear feasible in practice."

In closing, Public Citizen urges your committees to recommend that the FDA not approve the BLA for tanezumab. A drug like tanezumab, that accelerates the joint destruction of the underlying osteoarthritis disease that it is intended to treat but lacks any evidence of clinically meaningful benefit in comparison to use of a placebo or oral NSAID, obviously should never be approved by the FDA. We therefore urge you to vote no on question 3. No REMS would be sufficient to minimize tanezumab's risk of severe joint damage.

Finally, any further human studies of tanezumab in osteoarthritis patients would also be unethical. The use of the drug must cease. Thank

you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 4, your audio is connected. Please begin and introduce yourself. State your name and any organization you're representing.

DR. KHAN: Yes. This is Dr. Khan, Arif Khan. I'm a practicing psychiatrist in the Greater Seattle area. I'm medical director of Northwest Clinical Research Center, and an adjunct professor at Duke University and the University of Washington.

Essentially, I'm presenting some of the data from our center -- well, not our center completely, but this is some of the background information. I want to really state that I've been a principal investigator for over 600 trials the last 30 years. I don't do paid consultations for any pharmaceutical companies. I don't do any paid lectures for physicians or healthcare specialists for over 25 years, and this presentation was not requested, required, or supported by Pfizer or any other company. I've been a principal investigator

for seven trials, five of them for osteoarthritis, and a total of 246 patients were in these trials.

I'm presenting data from a clinical response from a publication last year. I was the author on it, published in Seminars in Arthritis and Rheumatism. With tanezumab, you don't find an immediate response, unlike opiates or analgesics. Patients noticed a reduction in osteoarthritic pain by the second day, statistically significant by the third day, and the pain can last up to 8 weeks after one subcutaneous injection.

Next slide, please. The left one is where patients completed their diaries. As you can see in graph A, by the second day you start to see that the drug separates. This is in Trial 1056. By the third day, it's definitely separating from placebo. The B really reflects and relates to patient evaluation in the office, which were done really at weekly intervals and not as sensitive as actual patient diaries. So there's a definite clinical response, which sustains up to 8 weeks, and some people up to 6 weeks.

The next one, the magnitude of response is very significant. The problem with many of our patients was that they started jogging, climbing stairs, and going on long hikes. Certainly, we even cautioned them. But that's what happened. The effect, clinical response, is dramatic.

In conclusion, what I can say is that I don't have access to full safety data, but my clinical sense is that tanezumab is definitely superior to analgesics, and opiates especially. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 5, your audio is connected. Please begin and introduce yourself. State your name and any organization you're representing for the record.

MS. PESCHIN: Thank you. My name is Sue Peschin, and I serve as president and CEO of the Alliance for Aging Research. The Alliance is the leading nonprofit organization dedicated to accelerating research to improve aging and health. The Alliance does receive financial support from

the product sponsor, however, we maintain several safeguards to ensure our independence.

I'm pleased to offer comment today, both personally and professionally. Both of my parents have severe osteoarthritis, which they have managed over many years with exercise and physical therapy; surgeries; one implanted medical device; one rollator walker; various OTC and prescription medications; and extra-strength doses of perseverance and humor.

The burden of persistent pain for older adults is significant. Approximately 65 percent of adults 65 years of age and older report suffering from pain, and 30 percent report suffering from chronic pain. Persistent pain in older adults results in reduced mobility, avoidance of activity, falls, depression, anxiety, isolation, and sleep impairment.

Osteoarthritis is one of the most common conditions causing persistent pain in older adults, and no current treatments exist to slow or reverse the destruction of joint structures that lead to

pain and disability for the condition. The chronic nature of the condition and the absence of safe and effective analgesics for late-stage osteoarthritis make this one of the largest areas of unmet medical need for older adults.

The potential promise of a new non-opioid treatment for those with moderate-to-severe osteoarthritis, for whom other treatments are ineffective or inappropriate, is encouraging. As the Arthritis and Drug Safety and Risk Management Advisory Committees review the application for tanezumab, we at the Alliance for Aging Research urge you and the FDA to carefully examine osteoarthritis patients' perspective on clinical outcomes of importance to them. And further, we ask you to specifically evaluate benefit-risk considerations for tanezumab to best serve this patient community's interest.

Risk-tolerance discussions should include pain management versus the potential for OA disease progression. Recent studies suggest that the risk of rapidly progressive OA with tanezumab was

greatest when co-administered with NSAIDs with higher dosage levels and in those with subchondral insufficiency fractures, all important considerations for clinician- and patient-shared decision making.

If approved, the healthcare providers prescribing tanezumab must be well informed about the medication's potential side effects and the patient population for which this treatment is most appropriate.

Last, we urge the sponsor, advisory committees, and the FDA to consider that older adults with chronic pain will sometimes overdo activity if they experience good days, potentially risking injury. Informing patients about their role in moderating activity levels while on treatment may be beneficial.

Thanks to all of you for engaging in this critical area of clinical development for older adults. Thanks.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 6, your audio is connected.

Please begin an introduce yourself. State your name and any organization you're representing.

MS. MARKSBERRY: Good afternoon. My name is Denise Marksberry, and I'm speaking on behalf of patients and the Global Healthy Living Foundation. The foundation accepts grants and total contributions from pharmaceutical companies, government, private foundations, and individuals. Its medical team has been briefed on osteoarthritis by independent scientists and physicians, as well as representatives from pharmaceutical companies.

I would like to start out talking about my own journey with osteoarthritis and how the lack of treatment options available to me has negatively impacted my health. I have had rheumatoid arthritis since I was 2 years old, so I'm accustomed to living with joint pain.

When I was 30, something new started to cause severe lower back pain. My doctor did a bone density test, which confirmed a diagnosis of osteoarthritis. At the time, my doctor did not want to put me on any treatment for OA because he

was worried about how my other medications for RA would react with any new treatments. However, between then and now, there have not been any significant advances in treatments for OA.

Like most patients with OA, I live in the middle ground between needing treatment and not having options available to me. As a result in the past 24 years, OA has led me to getting one knee replaced, which went terribly, horribly, and eventually I'll need both ankles replaced, but my bones are not dense enough to support the replacement.

Patients who have OA like myself have been living with this condition for years. The medication you're evaluating today offers us something that we have not had for decades, a treatment option designed to treat our disease. While it may not work for me, it offers patients like me hope that there is something more than just the status quo, and it fills a truly important unmet need.

I am seeking today to put a face to the

240 million patients worldwide who will immediately benefit from a new treatment option. I'm also here to put a face on the optimism that many patients have towards a medication that could potentially change their lives and give them their independence back. I have gone over 20 years with a condition that has been able to run rampant in my body on treatment. This medication offers me hope that finally may change.

Thank you again for the opportunity to provide comments on this issue. We will be submitting written comment to the formal docket. If you have additional questions, I'm available to answer them or you can refer to the Global Living Healthy Foundation advisor, Dr. Daniel Hernandez, MD. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 7, please begin and introduce yourself. State your name and any organization you're representing.

DR. PUCKREIN: Good afternoon. My name is Gary Puckrein. I'm president of the National

Minority Quality Forum, and I want to thank the FDA for the opportunity to present this afternoon.

The National Minority Quality Forum is a research and education organization based in Washington, DC. We have an institute for sustainable health care, quality and equity, whose focus is building sustainable healthy communities at the zip-code level, and we use data-driven research and evidence to drive change.

When we look at it, inside Medicare fee for service, in 2017, 25 percent of Medicare beneficiaries had arthritis and 90 percent of them had osteoarthritis. This problem is particularly troublesome in African American and Hispanic communities.

OA chronic pain and disability disproportionately affects African American patients compared to white. A recent meta-analysis show higher pain severity in blacks versus non-Hispanic whites. We also see that black and brown patients are less likely to receive comparable levels of pain management medications.

Research shows that medically-trained professionals also believe that people of color experience less pain and are more likely to abuse treatments.

We recently did a survey of minority, serving primary care physicians about osteoarthritis in Black patients, including pain management, current barriers to care, and strategies for increasing access.

This study was done among 41 physicians in 8 states. What we saw was lack of time with patients and lack of treatment options with what the providers indicated. When they looked at their patients, they saw cost, fees, knowledge, and comorbid conditions as barriers. They also saw systems problems, problems of lack of insurance, lack of specialists, and a lack of healthy food and transportation.

What the physicians at the end of the day suggested is that they needed more treatment options and ways to address structural racism in medicine, and we think this new therapy will offer them some new options that they currently do not

have. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 8, your audio is connected. Please begin an introduce yourself. State your name and any organization you represent.

DR. NICHOLSON: Good afternoon. My name is Dr. Bruce Nicholson. I'm a pain specialist, and I have been the director for the Division of Pain Medicine Lehigh Valley Health Network in eastern Pennsylvania for the past 30 years.

I am currently representing myself, as well as the Pennsylvania Pain Society, which is a group of interested and dedicated professionals across multi-disciplines related to the evaluation and management of patients with chronic pain. I have no conflict of interest in regard to my position today.

First, I'd like to thank everyone for this opportunity and also listening to the previous speakers, recognizing that there certainly is a tremendous unmet need in our community. As a clinician who has watched over the last 30 years,

in desperation and frustration, the lack of advancement in opportunities to manage patients with persistent chronic pain outside of the use of NSAIDs, as well as opioids; and recognizing that both of these have a positive, plus they have a harm side to them, knowing that between 15[000] and 20,000 Americans die from complications related to NSAIDs, the use of NSAIDs in the treatment of osteoarthritis; specifically understanding that randomized-controlled trials show little benefit after 6 to 8 weeks, presents a dilemma for any clinician who is asking a patient and a patient who's asking a clinician what the best management strategy is.

Opioids fit into a very similar category from the perspective of looking at randomized-controlled trials, showing little benefit outside of placebo for long-term management. And clearly we all, without having to go into this today, understand the potential societal related implications of opioid management.

So therefore, looking at the data and

listening to the speakers today, I think it's fair to say that we all have to balance the risk-benefit ratios. But without question, there's an advocacy and a need for better options for management, and tanezumab, without question, will give us another piece in our ability to manage patients that are refractory or may not be able to utilize current available therapies when it comes to addressing the desperate need for managing osteoarthritis. So I would thank you very much for the opportunity to speak today.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 9, please begin and introduce yourself. State your name and any organization you're representing for the record.

MS. REINERT: Good afternoon. I would like to thank the committee for their time and effort in considering this important issue. My name is Maddie Reinert, and I am here to speak on behalf of Mental Health America and our constituents.

Mental Health America is the nation's leading community-based nonprofit dedicated to

addressing the needs of those living with mental illness and to promoting overall mental health. Our work is driven by our commitment to promote mental health as a critical part of overall wellness. I did not receive any compensation for my time here today.

Chronic pain conditions such as osteoarthritis and mental health conditions are consistently the leading cause of disability worldwide. Studies have shown that the relationship between mental health conditions and pain is bi-directional. Among people with chronic pain, 35 to 45 percent experience depression, and depression, anxiety, and fear about pain are linked to both a higher probability of developing chronic pain and poor prognosis for recovery.

The relationship also exists in the other direction. Chronic pain has been found to increase the risk of developing depression. The experience of greater pain often results in worsening psychosocial stress and factors that contribute to worsening physical and mental health, such as

greater social isolation, disruptions in sleep, and reductions in positive health behaviors.

According to Mental Health America's online mental health screening program, people who reported having arthritis or chronic pain were more likely to screen positive or at risk for severe anxiety, severe depression, and PTSD than those without arthritis or chronic pain.

While existing medications are undoubtedly helpful for many individuals living with the chronic pain of osteoarthritis, for those to whom existing medications are not effective, the constant experience of pain can be devastating to both their physical and mental health. It is imperative that we continue working so that people dealing with chronic pain have more innovative, effective, tolerable, and fast-acting options to choose from when addressing their symptoms.

At MHA, we conducted an in-depth analysis of 38,000 individuals who took a mental health screen through the online screening program and indicated that they were living with arthritis or other

chronic pain. Many of their responses indicated significant distress and an urgent need for pain support. One person wrote, "My case is severe. I need something to work." When asked why they were searching for mental health support, another wrote, "I need real help and treatment to end the pain."

Even among individuals with access to care and medications, many were still not receiving the support and treatment they needed. One person explained, "I am a licensed healthcare worker injured and without options, despite an excellent education and desire to get well and work again in some useful capacity."

People are simply not receiving the treatment and support they need to live healthy and productive lives. We need to do more to provide additional effective options for the millions of people in this country struggling with the chronic pain of osteoarthritis and improve pain management to better address their physical and mental health needs.

In closing, we want to thank the committee

for its careful attention to exploring treatment options for chronic pain that can improve the lives of so many, and I'm happy to answer any questions you may have. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 10, please begin and state your name and any organization you're representing.

DR. MINA: Thank you very much. This is Dr. Mina, Maged Mina. I'm in San Antonio, Texas. I'm an adjunct faculty with the UT Health Science Center. I also serve as the vice chair of the San Antonio Pain Chapter and work closely with my colleagues across the state. I'm very thankful for giving me this opportunity, and I would chime in again with the last speaker. Mostly I'm presenting my pain practice as a private practice. I don't have any financial connections with tanezumab.

In essence, osteoarthritis, to reiterate, has the significant markers of causing disabilities for our patient populations and loss of function. We see patients. I co-manage my osteoarthritis patients with a rheumatologist and with

20 orthopedic total joint and spine surgeons across the city. I take care of them in several hospitals across the city.

We try to optimize their pain, but as my colleagues mentioned, some have failed multiple oral -- non-pharmacological, whether interventional or pharmacological approaches. Having another extra tool in our box definitely -- if tanezumab would be available to give us an extra tool.

Today, one of several patients that already shows -- a 36-year-old gentleman who works for a cable company is on disability because of osteoarthritis of his knee. Of course, his orthopedic surgeon is delaying a total joint replacement until he is 50. So he has to buy 14 years. He's concerned about opioids and failed other medications. This is one example.

To reiterate and chime in as the last speaker discussed the increase of comorbidities, cardiac issues, when these patients are not exercising, their cardiac comorbidities are increasing with congestive heart failure, chronic

artery disease, et cetera.

The psychosocial component with loss of functionality, this gentleman is now staying home. His wife is the breadwinner. The patients disassociate from society. Depression, anxiety, and loss of skills are key factors for those patients going through osteoarthritis and disability.

I would encourage the committee to look carefully at the pros and cons of tanezumab and if this is something available to be used in the treatment protocols for our patients. Thanks again. Be safe.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 11, please begin and introduce yourself. State your name and any organization you represent.

DR. McCARBERG: My name is Bill McCarberg. I do not receive compensation for my participation today. Over the last five years, I have been a clinical advisor to Lily and Pfizer, and I do not represent any organization. I'm a family

practitioner with 30 years of experience working in a large managed-care organization in San Diego. My interest today is to describe what I've seen in primary care related to arthritis.

Despite physical and pharmacological treatment options, these are not enough for many patients. We've already discussed acetaminophen. That doesn't work for many patients. Patients are well aware of the warnings about non-steroidals and are afraid of them. Joint replacement can be curative, but because of comorbidities, or even patient refusal because they're afraid of all the side effects of surgery, many patients opt not even to have surgery or even be evaluated.

I'm sure you're all aware of this, but many of these patients never get beyond me. They stay in my practice and are largely silent. We don't do studies on them, we are not aware that they're out there struggling, and we as providers don't even hear about them very much.

I want to write down -- because I was aware as talking today -- what I've heard from patients

and what they tend to tell me about their arthritis in their pain.

One said, "Nothing can be done." Another, "My doctor has tried everything." A third, "I'm old. My mother had a bum knee just like me. They couldn't do anything for her either." And the final one, "I had a hard life. What should I expect?"

These patients struggle but they don't complain very much, certainly not to me, their doctor. We do not hear from them, therefore we think they're okay. And as a provider, what we tend to concentrate on is something that has a metric I can improve, like hypertension or diabetes.

It's not that I'm not aware of their suffering or I'm not concerned about it. It's just that the pain kind of gets ignored. These are the patients that really decline. They withdraw. They stop taking care of their hygiene. They stay at home. They don't interact with their families. They don't go to Bingo when it's available. They

just wonder, and sometimes even wonder out loud, "How long can I put up with this? When am I going to die?"

This is a silent population. And anything that we can provide that can improve the quality of life for this patient population, I think we should take into consideration. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 12, please begin. State your name and any organization you're representing.

MR. BLADE: Good afternoon. I'm Kelvin Blade. Sophia Phillips and I are graduate students in Georgetown University's Health and the Public Interest master's program. We have no conflicts of interest. Our full testimony is available in the public docket.

Tanezumab is not effective. It's dangerous, and a REMS will not prevent harm. Tanezumab is only modestly better than placebo, and it is not superior to NSAIDs. The small benefits of tanezumab appear to wane over time; risks, however, persists.

In arthritis trials, tanezumab doubled the risk of severe joint problems and was associated with 94 percent of joint problems in normal healthy joints. Most harms occurred near or after the end of treatment, and the longest trial is only a year long. Risks may compound or accelerate after the first year.

We are concerned that tanezumab, an NGF antagonist, may worsen psychiatric conditions. NGF protects neurons that control memory and attention, and NGF levels are reduced in depression, schizophrenia, and dementia. Although one subject committed suicide, psychiatric harms were not assessed in these trials. In fact, subjects with neurologic or psychiatric diseases were excluded from the arthritis trials.

I'll now turn this over to Sophia.

MS. PHILLIPS: Testing a low dose of a drug in a low-risk population ensures that adverse events will be minimal. In a population so highly selected that it bears little resemblance to general population, harms caused by tanezumab were

still too high.

This drug is unnecessary. Many prescription and non-prescription alternatives exist. Moreover, the proposed REMS will not prevent harm. Counseling, monitoring, and imaging will not prevent joint destruction. Regular imaging of only hips and knees makes little sense when tanezumab can destroy any joint. Imaging may detect but does nothing to prevent joint damage. Also, the drug stays in the body for months, and no reversal agent is available.

In an ultra, low-risk population, 1 of every 41 subjects experienced a severe drug-related joint event. If tanezumab reaches the market, it could cause an epidemic of pain and disability, the very conditions this drug is meant to treat.

The committee has heard arguments that new options are needed. Tanezumab is not addictive, and NSAIDs and opioids are problematic. Certainly, new and improved drugs are needed, but new and harmful is not an advance. While it is true that tanezumab is not addictive, it's not very effective

either. Comparing it to opioids is wrong because opioids should not be used for arthritis. Tanezumab is far more dangerous than NSAIDs, which do not cause serious harm in 1 of 41 people who take them.

Overall, tanezumab is barely effective, dangerous, and unnecessary. The proposed REMS may detect harms but won't prevent harms. Tanezumab's substantial risks outweigh its elusive benefits. If this treatment is unleashed to the general population, an epidemic of joint destruction and disability may follow. Please keep tanezumab off the market. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker number 13, please begin an introduce yourself. State your name and any organization you represent.

MS. STAIRS: Hello. My name is Lily Stairs, and I am the interim CEO of the American Autoimmune Related Diseases Association, also known as AARDA. AARDA is the world's leading nonprofit dedicated to autoimmune awareness, education, advocacy, and

research. AARDA receives funding from individuals and corporations, including support from pharmaceutical companies, but have strict guard rails in place.

I first encountered AARDA as a patient seeking advice, and then worked as a volunteer, and later joined its board of directors. Now I am grateful to be in a leadership position that allows me to advocate for other patients, just like me, who are struggling to cope with the many demands of their conditions. Managing these demands whilst enduring ever-present chronic pain is difficult, if not impossible, to address adequately.

I'm here to speak on behalf of AARDA, but also I am speaking from the perspective of a three-time autoimmune patient that has lived the nightmare that is chronic pain. I am no stranger to chronic pain. At the age of 19, my total body arthritis resulted in a pain so severe that I could not dress or feed myself. The bleeding ulcers in my small intestine were so intense that I couldn't drink water without feeling unbearable harrowing

pain.

Most patients with an autoimmune disease experience some pain, but for many, pain is not just occasional; it's an unrelenting challenge that must be confronted each and every day. Of course, it is the patient who feels the greatest impact, but patients are not its only victim.

The consequences of chronic pain can invade the workplace, drain bank accounts, and disrupt relationships. From loss of sleep to loss of mobility, from loss of income to loss of hope, chronic pain greatly limits the quality of life for all who encounter it. Hope is essential for all patients, and new therapies are a powerful mechanism of hope.

Autoimmune patients know only too well that one size, or in this case, one medicine, absolutely does not work for all. That truth is a fact of life in our community. It is not unusual for autoimmune patients to have multiple conditions involving multiple body systems and requiring a complex medicine regimen and, yes, often suffering

from many types of pain. There are not enough therapies, there are not enough answers, but there is more than enough pain and suffering and need for better solutions.

Last year, AARDA held a webinar on pain. More than a thousand patients participated in the event. Over and over again, we heard stories and had questions about the inability of existing treatments to meet their needs, the negative impact of side effects from some current treatment, and the fear of addiction if prescribed opioids.

We followed up this event with a patient survey. Sadly, but to no surprise, our patient base told us that they had difficulty finding providers that understood their pain, and that their pain meds made them depressed and isolated, and ultimately decreased their quality of life. More than 50 percent of them told us they wanted new options for treating their pain.

On behalf of autoimmune patients, AARDA wishes to thank this committee for taking into consideration our multiple and complex needs, and

to remember that research and new treatment approaches are an essential beacon of hope for millions of people just like me. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker 14, please begin. State your name and any organization you represent.

DR. MALLAMPALLI: Good afternoon. I'm Dr. Monica Mallampalli, senior scientific advisor for HealthyWomen. Thank you for giving me an opportunity to speak today. I have no financial conflicts of interest, and I'm speaking solely on behalf of HealthyWomen.

HealthyWomen is the nation's leading nonprofit health information organization representing more than 18 million women. We provide consumers and healthcare providers accurate, evidence-based information about diseases and conditions, innovations in research and science, and changes in policy that affect women's access to treatment and care.

We thank you for the opportunity today to provide input in support of novel and non-addictive

treatment for chronic pain. I have also submitted written comments for this committee's review.

According to the CDC, chronic pain affects 1 in 3 women. An estimated 11.3 million women live with high-impact chronic pain in the United States. Osteoarthritis is a chronic pain condition. Several risk factors, including biological, sex and gender, age, race, ethnicity, genetics, and diet influence also osteoarthritis and its treatment.

For example, African American and Chinese women are at a higher risk for developing knee osteoarthritis, and African American women have greater pain and functional limitations compared to Caucasian women. They're also less likely to receive any or adequate pain treatment.

Chronic pain is difficult to treat in women, as women are 2 to 3 times more likely to have chronic overlapping conditions compared to men. Furthermore, currently available drug therapies for chronic pain conditions have limited efficacy and safety. Because multiple factors influence chronic pain, we need new treatments that will allow for a

personalized approach, ensuring that healthcare practitioners have several treatment options available for the diverse patient populations.

Importantly, providing novel treatment options, especially for osteoarthritis, allows women who are often juggling work, family, and caregiving to remain active while living with debilitating chronic pain. Novel treatments will also make chronic pain management affordable and accessible to more women, therefore, it is important to obtain patients' perspective and experience when developing novel treatments.

Last year, HealthyWomen joined 33 organizations in a letter, encouraging the FDA and NIH to ensure that new non-addictive pain treatments are available for patients, and to expeditiously and effectively move forward with the various provisions of the SUPPORT Act.

In conclusion, we want to ensure that the FDA understands the urgent need for novel non-addictive pain treatment for women, as the disease disproportionately impacts women, and

particularly women of color; recognizes existing biological differences and the influence of several factors, which makes pain personal; and includes women of all ages, races, and ethnicities in clinical trials to ensure that clinical trial data is evaluated and reported based on sex, age, race and ethnicity for outcomes and side effects.

Doing all of this will be critical for both providers and patients to make informed healthcare decisions together. We look forward to continuing to work with the FDA, and thank all of you again for the work you're doing to ensure that safe and effective treatments are available for chronic pain. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker 15, please begin. State your name and organization you're representing.

DR. FINK: Hi. My name is Dr. Ezekiel Fink. I am here on behalf of myself and also in the capacity of medical director of pain for Houston Methodist. I have done consulting work for Pfizer in the past, but I'm not receiving any compensation

for today.

I'm here to talk a little bit about the limited treatment options for moderate-to-severe osteoarthritis. There are limited treatment options for moderate-to-severe osteoarthritis. If you look at the different categories here, you can see that, for example, non-pharmacologic interventions -- exercise, weight management -- for chronic pain patients, especially for patients with osteoarthritis, those may not be things that they can do.

For non-steroidal, anti-inflammatory medications, or duloxetine, if you take opioids, those are medications that can have intolerable side effects for some patients. Although these are the agents that were compared against tanezumab, it's not fair to say, well, you should use that as a substitute instead because a lot of patients either don't respond to it or have contraindications to it. Surgery is typically something that we're trying to avoid, so these can be very difficult patients to manage.

Tanezumab does not have any of the side effects of NSAIDs or opioids, but it does have a noteworthy side effect profile. I was here for some of the earlier talks. That topic I'm not going to go over again, but this is a pretty substantial side effect profile that needs to be taken into account. However, I think it must be considered whether the risk-benefit justifies its use in certain patients, i.e., not everybody is the same, and chronic pain patients have a lot of different conditions, so it is worth considering.

For example -- and this is the age group that I think we'll be using quite a bit -- if you look at patients who are 65 years or older, over half of them report having ongoing pain issues or regular pain issues. Fifty percent have a diagnosis for osteoarthritis. Many of them have multiple chronic conditions. A lot of the pain is undertreated. Traditional recommendations can't really be followed through, such as exercise, and then there are drug-drug interactions.

So there are a lot of things to consider in

this patient population, and chronic pain patients oftentimes don't respond to a lot of the therapies that we've described here. So I think having something in addition to that for a select patient group is very valuable.

When going through this, I was reminded of the Cox-2 inhibitors and when those were taken off the market because of risks that were discovered after they were well in use. There were a large number of patients that had been taking Cox-2's that I had been seeing who were really disappointed and really didn't find that they had an alternative. And even after learning about the risks, they were willing to really sign any release form to continue taking that medication because it really solved the problem that was particular to them.

So there's certainly the bird's eye view, and there are risk factors that really need to be weighed carefully when starting this medication on any patient. But at the same time, in dealing with chronic pain, having additional options is really

critical, and I think that this does have a role in managing a certain population of chronic pain patients. Thank you so much.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker 16, please begin. State your name and the organization you represent.

MS. ANDWELE: Good afternoon, committee members. My name is Michele Andwele, and I thank you for the opportunity to testify today on my experience as a public health expert for the Arthritis Foundation, one of the nation's leading patient advocacy and education organizations for adults and children with degenerative and inflammatory arthritis and related pain conditions. The foundation receives patient education grant funding from pharmaceutical companies, including the sponsors, as well as government agencies and corporations.

I have worked for the Arthritis Foundation, managing patient education programs and resources, since 2013, and have been living with OA pain as a patient since 2006. I want to focus my remarks on

the data we have gathered about patient experiences with arthritis pain and preferences around pain management. The foundation does not take a position on specific medications, and I am not here to endorse or oppose approval of tanezumab, but rather to provide an essential viewpoint for your consideration, that of the patient.

With no disease-modifying drug for OA, symptom management is critical to daily functioning, health outcomes, and quality of life. The foundation launched a patient-reported outcomes assessment in 2019, and a hundred percent of respondents reported experiencing pain in the last 7 days, with an average pain score of 5, meaning moderately strong pain that can't be ignored for more than a few minutes, or with effort, can allow a person to work or participate in social activities.

The most common themes from our 2020 Deep Dive OA survey include 30 percent of patients report that their OA is not well managed, causing significant limitations or loss of hope for

options. More than half of patients are not likely to adopt a treatment to reduce pain if it would also cause further joint damage.

Patients report physical activity, heat and cold, and assistive devices as their most effective OA management strategies, and nearly a third say they have tried everything and still struggle with OA pain, and they want other non-surgery options.

This data reinforces a few key things I'd like to impart to the committee members today. There is a need for additional treatment options for joint pain, particularly for those who have tried everything else or have limitations in taking certain medications. No one treatment option is right for everyone, and the benefits and risks of each treatment should be carefully considered in consultation with a patient's healthcare provider.

Lastly, patient treatment goals should be a central part of the conversation when considering new treatments. Some patients may be willing to accept risks or trade-offs, depending on their disease profile and health goals. Thank you for

the opportunity to testify today.

DR. SUAREZ-ALMAZOR: Thank you.

Speaker 17, please begin. State your name and organization you represent for the record.

DR. HORTON: Good afternoon, committee members. I'm not representing an organization and have not been paid for my testimony.

Thank you for the opportunity to testify today on my experience living with osteoarthritis and managing pain. My name is Tonya Horton, and I have been living with osteoarthritis since 2017 when I was 47 years old. I will focus my remarks on what living with pain every day is like, how it has impacted my life, and the challenges of finding effective pain management.

I have pain daily. Some are good days; some are bad days. On the good days, the pain is there, but it does not prevent me from being able to go about my daily life. On the bad days, the pain is debilitating. On those days, I have to pause my daily life to spend the day in bed. I have very few great days, which are days with no pain.

Because I am in pain daily and because the severity of the pain varies throughout the day, I have to be more intentional with my day-to-day decisions. I have to plan my chores because I know that I cannot do everything at once. This includes chores that require me to leave the house. I also have to cancel plans from time to time based on my pain level.

Pain has also impacted my life in bigger ways. Living with OA pain is expensive. I used to live in a two-story house, and going up and down. the stairs was very painful. I recently purchased a house with first-floor living that has provided me with a lot of relief. When I am traveling, sitting in a regular coach seat on a flight is so painful that I pay for extra leg room or upgrade. When I use rideshare services, I always have to get a mid-size or larger vehicle because getting in and out of an economy-size car is painful.

My pain management journey has been difficult. I'm allergic to some NSAIDs and naproxen, so my prescription pain-relief options

are limited. I currently take Celebrex and Tylenol. I also do gentler forms of yoga that allow me to stretch my body and have found acupuncture to be helpful. Nothing works consistently, so it is really trial and error.

When I think about my pain management goals, I would love to have no pain, but that does not seem realistic. So my goal now is for pain to remain at a level that I can work and do other activities consistently.

I want to know that my pain will be under control, therefore, my goal is to find a pain therapy that will give me options in my daily life. Ideally, it would eliminate the pain. If the pain is not eliminated, it would be controlled so that I can engage in simple day-to-day activities like standing for long periods of time or walking around the block. I would not be limited in what I could do, and I would not be forced to live a smaller life than I am destined for. Thank you for the opportunity to share my story.

DR. SUAREZ-ALMAZOR: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. Before we adjourn, are there any last comments from the FDA?

(No response.)

DR. SUAREZ-ALMAZOR: No? Okay. Then I would like to thank -- go ahead.

DR. ROCA: This is Dr. Roca. I was just going to comment that I didn't have any other comments, and thank you. I couldn't get off mute quick enough. Sorry.

Adjournment

DR. SUAREZ-ALMAZOR: Okay.

I would like to thank the members of the public who shared their views and experiences in the open hearing, and the FDA staff and the sponsor for their presentations, and we will now adjourn the meeting. We will reconvene tomorrow, March 25th, at 10:00 a.m. Eastern time.

Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members. Additionally, you

should plan to rejoin tomorrow at 9:15 a.m. Eastern time to ensure you are connected before we reconvene at 10. Thank you.

(Whereupon, at 4:37 p.m., the meeting was adjourned.)