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

Thursday, March 25, 2021

10:00 a.m. to 12:49 p.m.

Meeting Roster

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C O N T E N T S

P R O C E E D I N G S

(10:00 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 today's 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. I am 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?

(No response.)

DR. CHOI: Ms. Hetlena Johnson?

(No response.)

DR. CHOI: Ms. Johnson, you might be on mute.

(No response.)

DR. CHOI: Okay. We'll come back to you.

Dr. Honczarenko?

DR. HONCZARENKO: Good morning. Dr. Marek Honczarenko, GSK industry representative, non-voting member.

DR. CHOI: Dr. Nason?

DR. NASON: Good morning. I'm Martha Mason. I'm a mathematical statistician at the National Institute of Allergy and Infectious Diseases.

DR. CHOI: Dr. Oliver?

(No response.)

DR. CHOI: Dr. Alyce Oliver?

(No response.)

DR. CHOI: Dr. Oliver, you might be muted.

DR. OLIVER: Good morning. This is Alyce

Oliver. I'm an adult rheumatologist at the Medical College of Georgia.

DR. CHOI: Thank you.

Dr. Pisetsky?

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

DR. CHOI: Dr. Richards?

DR. RICHARDS: Good morning. John Steuart Richards. I'm an adult rheumatologist at the VA Pittsburgh Healthcare System.

DR. CHOI: Dr. Singh?

DR. SINGH: Good Morning. Jasvinder Singh, adult rheumatologist at the University of Alabama in Birmingham.

DR. CHOI: Dr. Calis?

DR. CALIS: Good morning. This is Dr. Karim Calis. I'm director of clinical research and compliance for the National Institute of Child Health and Human Development at the NIH, and chair of the Intramural Institutional Review Board at the NIH as well.

DR. CHOI: Dr. Griffin?

DR. GRIFFIN: Good morning. Marie Griffin. I'm the general internist and pharmacoepidemiologist at Vanderbilt University in Nashville, Tennessee.

DR. CHOI: Dr. Habel?

DR. HABEL: Good morning. This is Laurie Habel. I'm an epidemiologist at Kaiser Permanente's Division of Research.

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: Collin Hovinga. I'm associate professor at the University of Texas at Austin, College of Pharmacy, and I am senior vice president of clinical and scientific development of a public-private partnership known as I-ACT for Children.

DR. CHOI: Dr. Kulldorff?

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

DR. CHOI: Dr. Meisel?

DR. MEISEL: Good morning. Steve Meisel, director of medical safety for M Health Fairview, based in Minneapolis Integrated Health System.

DR. CHOI: Dr. Nelson?

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

DR. CHOI: Ms. Robotti?

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

DR. CHOI: Dr. Cheng?

DR. CHENG: Hi. I'm Ed Cheng, and I'm a professor in the Department of Orthopedic Surgery at the University of Minnesota and practice in adult reconstructive surgery.

DR. CHOI: Dr. Horton?

DR. HORTON: Good morning. Dan Horton. I am a pediatric rheumatologist and pharmacoepidemiologist at Rutgers University in New Brunswick, New Jersey.

DR. CHOI: Dr. Katz?

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

DR. CHOI: Mr. O'Brien?

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

DR. CHOI: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Maria Suarez-Almazor, rheumatologist and clinical epidemiologist, University of Texas, MD Anderson Cancer Center.

DR. CHOI: Ms. Johnson, are you back? Can you hear me? If so, can you please state your name

and your affiliation, please?

MS. JOHNSON: Yes. Hetlena Johnson, consumer representative, community health research and lupus advocate.

DR. CHOI: Thank you.

Dr. Billy Dunn?

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

DR. CHOI: Dr. Bastings?

DR. BASTINGS: Good morning. This is 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 division director in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine, in the Office of Neuroscience. Thank you.

DR. CHOI: Dr. Borges?

DR. BORGES: Good morning. I'm Silvana Borges. I'm the acting deputy director in 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?

DR. HO: Good morning. My name is Martin Ho. I am the associate director of the Center for Biologics Evaluation and Research, and I will be presenting on behalf of the Center for Drug Evaluation and Research. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

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 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.

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: Okay. We will start the meeting now, but we have slightly changed the agenda. The sponsor has asked for 10 minutes to clarify some of the questions that were asked yesterday, so we will start by that. And there were a number of panel members that had raised their hands but did not get to ask their questions, so we will have another 10 minutes to continue with the clarifying questions to the sponsor from yesterday.

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 then your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

So we'll start with the presentation from the sponsor and then we'll move immediately to the clarifying questions that were pending from yesterday. Thank you.

DR. WEST: Thank you. This is Christine West from Pfizer. As indicated, we'd like to just clarify and address some questions that were raised that we didn't have an opportunity to address yesterday.

Could I see slide AH-1? The first is some

discussion with Dr. Cheng around healthy joints and different conclusions drawn by the FDA versus Pfizer regarding this data. To try to add some clarity to this, we annotated slide 17 from the FDA's presentation, which is shown on this slide, to separate the occurrence of the primary composite joint safety endpoint in Kellgren-Lawrence grade 0 and Kellgren-Lawrence grade 1, rather than including those together because they would not both be considered to be healthy joints.

Epidemiologic studies have shown that Kellgren-Lawrence grade 1 joints, which have osteophytic lipping, which would have some radiologic suggestion of osteoarthritis, are predictive of future progression and meniscal subluxation, so we think it's important to look at these two individually. We just made the separation; otherwise the data are as were shown by FDA. You can see, then, the occurrence of the events.

I point out that FDA's analyses of the composite joint safety endpoint, looking at the

occurrence in different grades of Kellgren-Lawrence grades, were based on only the affected joint, so not considering all joints that had these individual Kellgren-Lawrence grades.

If I could please have slide AH-2, that's a contrast to the way Pfizer has analyzed these data. We have considered all patients who have at-risk joints of Kellgren-Lawrence grade 0 or Kellgren-Lawrence grade 1. You can see in the top blue box, there's over 2,000 Kellgren-Lawrence grade 0 joints across our study population and over 1300 Kellgren-Lawrence grade 1 joints.

So what I'm showing you on this slide are, again, the orientation. Just to point out in the FDA slide, NSAIDs were on the left. I've now kept an orientation like Pfizer's slides have done, so NSAIDs are on the right now.

You'll see placebo, tanezumab 2.5 milligrams and NSAIDs broken down to the primary composite endpoint by Kellgren-Lawrence grade 0 and grade 1. You can see the percentage of patients who had at least one Kellgren-Lawrence grade 0 or 1 across the

treatment groups. You can see that that ranges from about 45 percent up to 69 percent across the treatment groups.

We've then shown the primary composite endpoint with the breakdown of the components of the endpoint and the occurrence of total joint replacement. You can see, one, placebo Kellgren-Lawrence grade 1 went to total joint replacement; 2.5 milligrams, it was 0.3 percent in the Kellgren-Lawrence grade 0, so again those without radiographic evidence of osteoarthritis.

Those are then broken down into RPOA-1 and one osteonecrosis case. The patient with osteonecrosis had alcoholic liver disease, which could have predisposed the patient to developing osteonecrosis.

Within Kellgren-Lawrence grade 1, RPOA-1, all of the events with tanezumab 2.5 milligrams were RPOA-1. None of those joints went to total joint replacement. With the NSAIDs treatment group, there was one, the primary composite endpoint in the Kellgren-Lawrence grade 0, and that

was a subchondral insufficiency fracture. And lastly, Kellgren-Lawrence grade 1 NSAIDs joint, we have one RPOA-1 event.

So you can see from looking at the primary composite endpoint, it's 0.3 percent for tanezumab 2.5 in Kellgren-Lawrence grade 0 and 0.1 percent in the Kellgren-Lawrence grade 0 NSAID.

If I could have slide AH-3, please, we then look at the risk difference using those individual incidences, and you can see now illustrated on the left the Kellgren-Lawrence grade 0 for the primary composite endpoint and all of the components. The risk difference versus NSAIDs is 0.1 percent, and no events of total joint replacement, and no events of RPOA type 2. On Kellgren-Lawrence grade 1, the risk difference is less than 1 percent relative to NSAIDs, 0.8 percent, all RPOA type 1 and no total joint replacement.

I'd now like to move to another topic. Slide up, please. Please pull up slide JS-712. I'd now like to move to the topic of whether the risk increases over time. I showed you some

different analyses yesterday to evaluate the occurrence of events over time, and we've done this analysis by looking at the occurrence of the events within the imaging intervals because obviously we can detect these events when the images are taken. These intervals represent those intervals, up to week 24, after week 24 through week 56, and after week 56.

In the table, I'm showing you the occurrence of the primary composite endpoint, so all of the components for the tanezumab 2.5 milligrams and the NSAID treatment group, and then the forest plot on the right shows you the risk difference, overall and by period.

If we follow those risks differences down on the far-right side of the slide, you can see that in the first period, its 1.0 risk difference, 1.2 percent in the 24 to 56 week, and after week 56 is when treatment has stopped. The risk difference is 0.9 percent.

I'd like to point out, in the week 24-through 56-interval, which is in the middle, you

can see both tanezumab 2.5 and NSAID, and that was the highest incidence of joint safety events. So the trend is very similar between these two treatment groups. That's why you're not seeing differences in the risk difference over time.

Right now, could I please have slide JS-46? There was quite a bit of discussion about the concordance between the adjudication committee and the central reader. As the FDA acknowledged, we have indicated, and I did in my presentation, the remit of these two groups were different. The central reader was designed to be very sensitive in their reading and surveil for events that may need follow-up and adjudication.

The adjudication committee's purpose was to review those events and determine the outcome. Much like is done in clinical practice, the adjudication committee reviewed the imaging as well as clinical information to make their determination.

This particular slide shows you on the left, if we look at the incidence of the events for the

primary composite endpoint and the individual components broken down for the central reader's assessment and on the right is the adjudication to be assessed, you can see the pattern is very similar.

The FDA indicated on page 180 of their briefing document that the conclusion about the joint safety risks associated with tanezumab treatment relative to placebo and NSAIDs does not change when looking at the assessments of the central reader versus the adjudication committee.

It was pointed out there were different numbers of events between the central reader and the adjudication committee. That's true; 241 events versus 145. The adjudication committee had approximately 29 percent of those adjudicated as normal progression of OA and 13 percent adjudicated, the difference between the two. So I'm giving you percentages of the entire 241; 13 percent, then, were other.

Again, other was a category that the central reader did not have available to them because they

did not have information about medical history and other things to consider other clinical information that the adjudication committee did. So on balance, we think that whether you look at either one of these assessments, the overall conclusions, we concur with FDA that the conclusions are the same.

I would now like to move to slide AH-6, please. I'd like to just circle back to a question Dr. Nason asked of me yesterday, and I provided some information but I did not have all of the details.

So we have gone back to look at the question, which was whether the at-risk set of patients used for our Kaplan-Meier analyses and other analyses of rapidly progressive OA type 1 data included patients who would not have had an opportunity to have an RPOA type 1 event because of their baseline severity, whether it be Kellgren-Lawrence grade 4 or their joint space width was less than 2 millimeters, which is the definition for RPOA type 1.

I'd just like to clarify that any joint could be at risk for RPOA type 1, so we included patients, and all joints again could contribute to that. So it's not just the index joint potentially being at risk.

We went back and looked at our data, and there was only one patient who was in the tanezumab 5-milligram treatment group who had severe enough osteoarthritis in all four major joints, so hips and knees, that would have precluded them from being able to have an RPOA type 1 event. So based on that, we don't think any new analyses need to be performed, and the denominator would be appropriate for the analyses we have done.

I'd like to ask Dr. Hickman to provide a few additional clarifying comments, please.

DR. HICKMAN: Yes. Thank you, Dr. West. And thank you for the opportunity to clarify our REMS program. We have high confidence in the REMS program. It is not just a surveillance program.

As Dr. Verburg mentioned in his introduction yesterday, we had almost finished a thorough

phase 3 program when the risk for RPOA emerged, the safety data from those studies to develop risk minimization measures, which were then used in the subsequent phase 3 through program. And now with input from external experts, we have adapted these measures to make them appropriate for real-world use.

I think it's important to note that with these risk minimization measures in the post-2015 clinical trials, at an incidence of 0.4 percent for RPOA type 2, which wasn't different from the NSAID group, and an incidence of RPOA type 1 that was only 1 percent higher than the incidence with the NSAID group, no REMS can prevent all events, but our REMS is designed to do a number of very important things.

Most importantly during that, prescribers and patients were educated about RPOA, and the associated risk minimization measures is the key to minimizing RPOA. The required counseling of patients will also ensure that shared decision making has taken place.

If we can please bring up slide RE-5? This slide summarizes the key risk minimization measures that were successful in reducing risks for RPOA in the clinical trials and that were incorporated into the postmarketing measures. The REMS requires baseline radiographs of the knees and hips to identify pre-existing RPOA and risk factors for RPOA. This is to ensure that higher risk patients aren't treated.

Patients that don't have a satisfactory clinical response after receiving doses of tanezumab stopped treatment. This will help minimize unnecessary exposure. Prescribers need to know all of the data regarding NSAIDs.

Chronic use for greater than 90 days at full prescription strength led to an increased risk for RPOA, however, the educational materials will also provide clear guidance on the appropriate acute use of NSAIDs if needed for injury or illness. Use of NSAIDs for 10 days or less in an 8-week period was not associated with an increased risk for RPOA in data from both the pre-2015 and post-2015 studies.

Appropriate monitoring will ensure early identification of cases. Patients and prescribers should [inaudible – audio gap] know about this. About 30 percent of patients had symptoms before they had a diagnosed event. Early identification is important, as none of the patients that discontinued the RPOA-1 in the clinical trials progressed on to have bone damage or RPOA type 2.

Very importantly, if treatment is going to continue beyond one year, benefit-risk should be reassessed, including review of radiographs of the knees and hips. Prescribers must sign the patient continuation form, and they must attest that the discussion with patient has occurred about the lack of efficacy and safety data beyond one year.

DR. SUAREZ-ALMAZOR: Dr. Hickman?

DR. HICKMAN: Yes. I'm almost done.

DR. SUAREZ-ALMAZOR: Okay, because you have exceeded the allocated time, and this is new material.

DR. HICKMAN: Thank you.

In these refractory patients, we would

anticipate that those still receiving [inaudible - audio gap] tanezumab at one year are receiving benefit, but if not, this is an opportunity to reassess whether they should continue treatment. All of these measures can be incorporated into the current standard of care for OA patients, and we'll work together to ensure the risk for RPOA is minimized. It's important to remember that we will also be assessing the REMS program shortly after initiation and can make any needed changes. Thank you for that opportunity.

Clarifying Questions (continued)

DR. SUAREZ-ALMAZOR: Thank you.

We will move now to clarifying questions. There were three panel members that had raised their hands. So we will answer their questions, and if we have time within 10 minutes, we may take some additional clarifying question.

Mr. O'Brien?

MR. O'BRIEN:. No. My question has been answered. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Singh?

DR. SINGH: This is Jasvinder Singh, University of Alabama, Birmingham. The clarifying question I had for the sponsor is, was there an analysis undertaken whereby the peripheral edema and the mild but self-limited neuropathy events were perhaps combined with RPOA-1, RPOA-2, and TKA or TDA, and a timed-event analysis done using the data from the NSAID study, which is a longer study?

I'm sorry if I missed that. I'm not sure if that was undertaken or if you have any thoughts about that.

DR. VERBURG: Thank you, Dr. Singh. This is Ken Verburg from Pfizer. We have not conducted an analysis that combines all of those components into one category or cluster and then run an analysis. But we have done components of it, evaluating the concordance or concurrence of patients that had both abnormal peripheral sensation of that, as well as a joint safety event. But those analyses are somewhat confounded by time. The events don't necessarily occur concurrently.

We've also assessed patients reporting an

adverse event of abnormal peripheral sensation and the occurrence of peripheral edema. So we have addressed some of these components, but to your suggestion, no, we did not have an analysis that takes all those factors into account in one announce.

DR. SINGH: Thank you. The reason I brought that up, Dr. Verburg, is despite the large sample size for the 1058 study that, compared to NSAIDs, the number of events in RPOA-1 and 2 had a separate category and TJA as a separate category, it is not large enough to, A, look at predictive factors that may be associated beyond the NSAID concurrently used that you concluded, based on the data from this and other studies; but not from this study, from other studies.

Therefore, when you increase the sample size with this outcome, which potentially has the same underlying mechanism, it might get some insights to finding factors that might predict this neuropathic, neurogenic blockade-associated adverse event. So that was the point behind that. Thank

you.

DR. SUAREZ-ALMAZOR: Dr. Pisetsky, you had a question yesterday?

DR. PISETSKY: Yes. This is perhaps speculative. I would appreciate from the sponsor an idea of what they think the mechanism is of the rapidly progressive disease.

Is this the target? Is it the fact that it's a biologic, so that the analgesia is prolonged? I think it's relevant in terms of developing a risk management strategy if you have some sense of the mechanism.

DR. VERBURG: Yes, thank you for that question. This is Ken Verburg again from Pfizer. As we indicated yesterday, given our clinical observations that rapidly progressive osteoarthritis was associated with both tanezumab and NSAIDs in our program, and the literature reports of similar associations with intra-corticosteroids, our working hypothesis is that pain relief results in altered joint mechanics, producing high biomechanical strains.

So our hypothesis is sort of central to biomechanics that really exceeds the properties of the tissue that leads to rapid destruction.

Could we please show slide JS-646, please? To give you a visual of what this looks like in terms of a diagram, exactly how this occurs remains unknown, but the change in joint mechanics or loading seem like precipitating factors that lead to joint damage directly, or more likely because of the patterns of joint safety events that we see in combination with joint specific factors.

One of those factors is the presence or absence of osteoarthritis. Another one could be the subchondral bone integrity, whether the patient has a SIF or has microfractures in the joint bones; or it could be just trauma that's not evident.

We don't have any evidence that the hypothesis of the joint damage with tanezumab treatment is the result of direct metabolic effects, cartilage turnover, or adverse effects on joint innervation. We studied this issue in preclinical in animal models, including non-human

primates, and have found virtually no evidence of any joint pathology in animals at very high multiples of the clinical dose for periods of duration [inaudible – audio gap] for quite some time. Slide off, please.

I'd just like to go to Dr. Schnitzer for just one minute to provide some perspective on this as well, as he's had a research history in this area.

Dr. Schnitzer?

DR. SCHNITZER: Thank you, Dr. Verburg.

I want to just say that while I've been compensated by the sponsor to be here today, I have no financial interest in the outcome of the meeting.

We did studies back, believe or not, in 1993, looking at the effects of non-steroidal anti-inflammatory drugs in patients with OA in terms of case studies looking at loading. And what we showed very clearly was that 15 out of 18 individuals who received NSAIDs increased loading in the medial compartment. Many of these

people had medial knee OA, a result of increased adduction moment that occurred due to the decrease in pain.

These studies have been now replicated at least half a dozen times. The major person involved in this was Tom Andriacchi, and there's no question that relieving pain at the knee in someone with osteoarthritis will significantly increase their loading.

So I think that's a very strong indication that the biomechanics are what's driving a significant aspect, particularly, of the RPOA-1 events.

DR. PISETSKY: Can I ask, what is the implication for the patient if that's true?

DR. SCHNITZER: Well, I think the implications for the patients are really hard to know. I think there's a trade-off between pain relief and continued evolution of changes in the joint. I think we've seen this clearly in the anti-NGF programs, which is that the greater the pain relief you provide, the greater the incidence

of these events.

So I think the really critical issue is finding the sweet spot, finding the place where you can get enough pain relief to be clinically meaningful for patients and still end up with as a lower rate of these events as possible. We've seen these rates with non-steroidal anti-inflammatory drugs just as well as we do with anti-NGFs.

So the point is -- and I think this was well demonstrated with the indomethacin data roughly the same period of time; effective pain relief will drive this. There's just a trade-off, I think, and it's really critical, therefore, to find the right dose of an analgesic agent when we're dealing with this type of situation.

I think the other thing --

DR. SUAREZ-ALMAZOR: Okay.

Dr. Schnitzer, yes, we really need to --

DR. SCHNITZER: -- exclude people with pre-existing conditions to preclude that. So thank you.

DR. PISETSKY: Thank you. That is all for

my questions.

DR. SUAREZ-ALMAZOR: Yes. We need to get going. I'm only going to take two more questions, and the first one is from Dr. Richards, and the other one from Dr. Hovinga. Please, just a single question, and from the sponsor, a straightforward answer because we really need to move on.

Okay. Dr. Richards, first.

DR. RICHARDS: Thank you. John Richards. I may have missed this yesterday, but was there an explanation for why there wasn't a longer term extension open-label of Study 1058 going beyond the 56 weeks in a drug that we're considering using for many years? Thank you.

DR. VERBURG: Yes. This is Ken Verburg from Pfizer again. I think the simple answer is when we discussed the components of the clinical development program with the FDA, following the release of the clinical hold in 2012, we discussed the length of the program in terms of duration of studies, and both parties agreed that that appeared to be acceptable at that time.

Of course in retrospect, and looking at the occurrence of the joint safety events now, it would have been very useful to have some additional data that goes out beyond multiple years. That's not uncommon in clinical development programs, and as Dr. Hickman mentioned yesterday, we're committed to do additional work to evaluate and characterize the longer term safety.

But in the meantime, we feel like the REMS program offers some confidence and some reassurance that patients undergoing treatment for multiple years of therapy will be thoroughly evaluated by their physician before doing so.

DR. RICHARDS: Thank you. That's all I have.

DR. SUAREZ-ALMAZOR: Dr. Hovinga?

DR. HOVINGA: Hello. This is Collin Hovinga from UT Austin, I-ACT for Children. I had a question about the REMS program in and of itself, and perhaps this was stated, but I wanted to clarify.

As individuals are participating and

receiving the medication, is there any formal documentation that has to be done? Is there any sense of accountability that people are -- besides just acknowledgement?

I think it was mentioned yesterday by the FDA that there might be concern from a practical sense, that even though people were advised to do this, there was really no way to ensure that people were staying within the bounds of the limitation. So I wanted to clarify if there was any anything that helps support the individuals or make sure that the REMS will be followed by the patient population. Thank you.

DR. VERBURG: Sure. I'm happy to answer that question. Yes, I'll turn it over to Dr. Hickman, and she can provide additional details.

DR. HICKMAN: Yes. Thank you very much. During the REMS program, the formal documentation occurs at the enrollment process where prescribers must sign the enrollment form, and patients must sign enrollment forms saying they understand the

requirements. And then, again, we have the formal form at one year, that they have to document that the additional benefit-risk counseling has been done and radiographs have been conducted.

So in between times, a patient will be required to be coming back in for each injection, and that will be the opportunity for the counseling.

Now, we don't have formal documentation of every visit, however, what we wouldn't be doing in our REMS assessment plan, which I can go into more detail if you'd like -- but during the REMS assessment plan, we will be able to assess using electronic healthcare data, whether the radiographs are being conducted. We will be able to determine whether NSAID prescriptions are being taken. We're going to audit the healthcare settings and find out if they're doing what they're supposed to be doing.

The other thing is that we're going to have surveys of both prescribers and patients to make sure they understand the requirements and that they're implementing them. So we do have a number

of evaluations that will go in, and those will be documented officially. We will be reporting back initially at 6 months to FDA, and then at 12 months, and annually thereafter. So we do have a very thorough assessment plan that will be looking at these factors.

DR. HOVINGA: Thank you.

DR. SUAREZ-ALMAZOR: Okay. Thank you.

We will now proceed with a charge to the committee from Dr. Rigoberto Roca.

Charge to the Committee – Rigoberto Roca

DR. ROCA: Hi. This is Dr. Roca. Thank you, Dr. Suarez-Almazor.

Can we have the questions put up on the screen?

As I mentioned yesterday during my opening comments, what I had hoped, as you listened to the presentations, was that you would keep the two major items in the back of your mind with respect to what I was hoping to have a discussion about today. The two items are really related to whether the risk of the joint-related adverse reactions

have been adequately characterized.

That would be the first discussion item that I'm hoping to have you undertake, and within that, particularly the characterization of the risk over time, that will be part of the discussion, and also whether there's information regarding the long-term prognosis and the outcome of the patients who developed joint-related adverse reaction. Thank you.

So that would be discussion point one. The second item for discussion relates to the REMS, whether the strategies are effective in mitigating the risks and also whether you believe that the proposed risk mitigation measures are adequate to identify the adverse events; also, whether you feel that the strategies can be successfully implemented in routine clinical care; and lastly, whether there are any additional risk mitigation components that you think would be useful and could be added to reduce the incidence of structural joint damage.

So those are the two discussion items. The third is a voting question, and with this one we

try to write it up as a straight-up yes or no. And it relates to whether the REMS, which have been proposed by the applicant, will ensure that the benefits outweigh the risks.

After the vote is tallied, if you have voted no, we will be interested on any other studies or information that you think would be needed to address the risks of tanezumab.

One of the things I would like to point out is that we try to make this question relatively straightforward and, basically, a yes or no. If you happen to feel that you need some clarification on the question, I think that you can ask, but I do ask you this.

If you choose or you feel that you need clarification on this question, which again I think is relatively straightforward -- but if you feel that you need clarification, please make sure that any comments, or observations, et cetera, that you may make will not reflect how you intend to vote. Any comments or observations regarding the issues really should be discussed during items 1 and 2

when you're undertaking discussions about the issues that we would like to have discussion about.

So I just want to make sure that if you feel that you have to ask a question about question 3 and the vote, to make sure you do not in any way reflect your thinking at that point as to how you intend to vote. Thank you.

Dr. Suarez-Almazor, I'll turn it back to you at this point.

Questions to the Committee and Discussion

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

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

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

we will open the question to discussion.

Question number 1. Discuss whether the applicant has adequately characterized the risk of joint-related adverse reactions that may be caused by tanezumab, A, characterization of the risk of destructive arthropathy over time, whether the risk continues to increase with ongoing tanezumab treatment, whether a risk ceiling is reached after a set duration of treatment; and evaluation of long-term prognosis and outcome in patients who develop a joint-related adverse reaction and subsequently discontinue tanezumab.

Are there any questions about the wording?

(No response.)

DR. SUAREZ-ALMAZOR: I don't see any hands raised. So if there are no questions or comments concerning the wording of the question, we will now open the question to discussion. For this particular question, I think we can group A and B together, as they seem to be quite interrelated in the discussion, so we can start now. Please remember to raise your hands.

Dr. Griffin?

DR. GRIFFIN: Marie Griffin. I really do feel like there's not -- because this is a drug that may be used for years, and I think we've learned about this from other drugs that are used for years, that we really don't know about the cumulative effects over time. One percent or 2 percent sounds low, but when you add that up over 5 or 10 years, that's a lot, and it may be more than that. So I think that's a concern.

As far as B, I think we don't know about whether these changes make getting a joint more complicated. If it were just the progression of a joint that was already very bothersome to the patient, that's one thing, and they're getting a procedure that they would get anyway. But some of these procedures are on other joints, and we don't know if the procedures are more complicated than they would have been without the drug. So I think those are two of my concerns. That's all.

DR. SUAREZ-ALMAZOR: Dr. Singh?

DR. SINGH: Jasvinder Singh, University of

Alabama, Birmingham. I think the discussion regarding 1A, we just recognize that, in retrospect, a longer study would have been probably more informative, but such data do not exist. It's not possible to address this concern.

At what rate does the risk keep going up after 52 weeks or 52 plus a handful of weeks in the observation period? Obviously, some of these processes take several years, if not decades, to go from a radiographic OA stage to a total joint replacement.

So to my knowledge, from the discussion of the data we've seen, we don't quite know if a risk ceiling is achieved, and we have no idea about the time that that's achieved and the rate of increase beyond 52.

Regarding the second one, I think that even though I think some data were presented by the sponsor with regards to discontinuation within a short span of a randomized-controlled trial and/or an observation period in the short extension, we don't know the long-term effects of discontinuation

on the progression of RPOA or joint-related adverse reactions.

I think somewhat related to that is the discrepancy between the adjudication and the central reader, where specific criteria were set up, yet there was some discrepancy that noted that the patterns are similar. That also brings up some challenges in interpreting these data. So I don't know whether a much longer study of several years, with some additional thinking and/or much larger samples, could perhaps address, but it would have to be very large.

There would have to some additional insights into what Dr. Pisetsky brought up with regards to the understanding of the pathophysiology and underlying biology of what leads to this RPOA, what factors shall we stratify people on, and what sort of patients do we need to get into those long-term studies. Along that needs to be, is there a spectrum between neuropathy and RPOA-1, RPOA2, and TJA, and those sort of things.

So I think there are several very important

questions brought up by these studies that remain to be answered and are concerns. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Oliver?

DR. OLIVER: Hi. Alyce Oliver, Medical College of Georgia. Dr. Singh and Dr. Griffin essentially said the same thing that I was going to; that we only have data from one study, Study 1058, that showed the 7 subcutaneous injections and then time points a little bit after that 48 weeks. But we still don't know the cumulative risk of the drug on the osteoarthritis.

DR. SUAREZ-ALMAZOR: Dr. Cheng?

DR. CHENG: Thank you for the opportunity to comment on these discussion points. It's my opinion that the applicant did not adequately characterize the outcome of patients with the CJSE composite score events over time; that is, they only addressed whether or not the patients underwent a total joint replacement. Well, not only; that is one outcome metric they showed.

I have to say that as a surgeon, total joint arthroplasty is an outcome metric that is very

unreliable and flawed as a threshold for proceeding with a total joint replacement. It's highly variable, depending upon the patient, circumstances, surgeon's opinion, and the native culture, where the patient resides, as the applicant stated themselves.

I do think the FDA did show that the rate of events rises over time. The slope increases on their Kaplan-Meier plot, and it has not clearly plateaued at the end of the trial follow-up date. This was in the slide 15 and 16 that Dr. Pokrovnichka showed.

I appreciate the additional data that the applicant presented today, however, it is not actuarial data and not as reliable as the Kaplan-Meier plots presented by the FDA, which most would consider is the gold standard for reporting the outcome of a time-dependent factor. With a new class of therapy, which this represents, I'd recommend that we'd be cautious about making any approval statement.

In regards to part B, I don't think the

applicant or the FDA, either one, has adequately shown the long-term prognosis because of the limited time of the trials that are enforced and the limited follow-up as well. Thank you.

DR. SUAREZ-ALMAZOR: Mr. O'Brien?

(No response.)

DR. SUAREZ-ALMAZOR: Mr. O'Brien?

MR. O'BRIEN: Yes. Sorry.

I agree with all the comments that have been made so far for sure. I think my concern comes with the Catch-22 nature and the etiology of the adverse events, the RPOA, and the lack of dealing with that in terms of identifying the risk-benefit for the patient.

Patients are involved with two things, how they feel and how they function. So we have a situation that we have a drug that makes them feel better, so they're going to function more; yet that function causes more adverse events, which was expressed in the sponsor's responses today in terms of their working hypothesis of what's causing this RPOA.

Yet, I look in the literature, and I see that that hypothesis was actually around and published in the '90s, that same thing. And yet, I was disappointed that there was no attempt within the studies that I saw to identify those who, in fact, have increased loads on the joint. We're only looking at markers to see whether or not they have it. We're doing nothing, really, in a preventive nature to isolate whether or not the working hypothesis is real or not real.

So I'm very concerned about that in terms of identifying, because the nature of the patient is going to be, if I feel better, I'm going to function more. And if we're telling them that, inevitably, you're going to end up, therefore, with the surgery you're trying to avoid, then we really have a Catch-22 here.

DR. SUAREZ-ALMAZOR: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. Regarding A, I think we have seen the characterization for the duration of the trials, and we have seen how there is a higher rate or

number at the beginning of the follow-up probably because of those susceptible are going to have the events at the beginning. And we see that the rate attenuates over time, but that the cumulative risk is still ongoing, at least until the end of the trial. So as Dr. Griffin was saying, I think with the data we have, we will expect that the numbers might still be accumulating over time, perhaps.

Regarding B, I would like to add that one aspect that may be important to discuss the REMS later is that for the long term, once the radiographic deterioration is identified, discontinuation of the treatment might not reverse the damage, and I think that's going to be important for the REMS.

I would love my radiologists, rheumatologists, and colleagues on the team to comment on that, that once a radiographic deterioration is identified, whether discontinuation is going to reverse it.

Ones last point regarding the biomechanical hypothesis, which I found fascinating. I wonder

how can we explain that since there is no difference in pain and relief with NSAIDs, why would the treatment have not better pain control, but more outcomes due to the increased movement and due to the reduction in pain. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Kulldorff?

DR. KULLDORFF: Hi. This is Martin Kulldorff. I think that the applicant has made a very thorough study of this drug. Both the applicant and FDA have done a very thorough analysis and representations of both the efficacy and adverse reactions.

It's very clear that there's an increased risk for joint adverse reactions from the drug, but we can't necessarily expect to know every detail about the adverse reactions. I think compared to many other advisory committee meetings, we know more about this drug than in many situations. In terms of whether or not it will be here, I think that is the question mark. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Honczarenko?

DR. HONCZARENKO: Marek Honczarenko. Thank

you. I would like to provide a certain industry perspective, obviously from the point of view of how we conduct the clinical trials, and what is possible and what is not possible.

For us, always, proper examination of the events with very low incidence, I have to tell you that, essentially, the safety events are of very low incidence, especially the difference between standard of care and incidence of rapidly progressing OA-1 of tanezumab versus NSAIDs. It's 2.3 versus 1.1 percent. This obviously is even lower for probably more significant rapidly progressing OA-2, which is 0.4 for tanezumab and 0.1 for NSAIDs.

We have significant limitations, obviously, how we can design and how long we can conduct the trials in the rheumatology field. It's not a cardiovascular disease, when we can enroll tens of thousands of patients.

But having said that, this program obviously, historically, is a massive program with 17,000 patients across 39 studies, which were

enrolled, and almost 10,000 patients treated in the context of well-controlled phase 3, with over thousands of patients having long-term follow-up.

I think in the context of clinical development, this is a certainly well-controlled program. Also, considering the patient population, which is a very high unmet need, which tanezumab is proposed for treatment, it's not the first line. And in the context of the risk management program and potentially postmarketing trials, I think from a purely industry clinical development perspective, this program is as well controlled as we can ever design for rheumatology indications. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Dr. Nason?

DR. NASON: Martha Nason. Thank you. I agree with my colleagues who have expressed the need for longer term data and that there's no clear evidence, to me, that a risk ceiling has been reached rather than that it continues.

But the one question maybe I should have asked the sponsor, or maybe I'm just suggesting to

the sponsor is if it is possible to get any longer term follow-up on the participants who were enrolled in the post-2015 studies. It wouldn't be the first time that participants from previous studies were reached out to and asked if they'd be willing to join a follow-up study or even just provide their medical records or some updates.

I think that could be really reassuring potentially, or illuminating anyway, if there was a way to find out what had happened to those participants or as many of them as you could find since their inclusion in the study.

DR. SUAREZ-ALMAZOR: Dr. Nason, you're done with your comment?

DR. NASON: Yes, sorry. I'm done. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Thank you.

I believe Pfizer wanted to make a comment. Please keep it brief and with no slides or additional materials.

DR. VERBURG: Yes, very quickly. Ken Verburg from Pfizer. We wanted to make a comment

about the interpretation or the analysis of the Kaplan-Meier plot. I'm going to go to Dr. Glenn Pixton to provide just a comment or two on that.

MR. PIXTON: Sure. Thank you, Dr. Verburg.

This is Glenn Pixton, Pfizer statistics. We do agree that the Kaplan-Meiers are a good way to look at data over time. We just wanted to point out the issue that we have with our NSAID is that the events we are finding are usually found through imaging, so we know when an event was detected but not necessarily when it started.

So our presentation of the three time periods, showing our data over the three time periods, is an attempt to try to group that Kaplan-Meier data into imaging-related intervals to make the data more interpretable in that sense. And I guess what we see is that in both the Kaplan-Meier and these period analyses, they indicate that both tanezumab and NSAIDs have the events in all of the time periods, and that there's also a lower rate for the treatment groups, for all of the treatment groups in that final off-treatment

period. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Dr. Pisetsky?

DR. PISETSKY: With respect to the first point, I have concern about how much we know about this destructive arthropathy and the risk of adjunctive therapy. Most people with osteoarthritis are going to receive something else, even if it's an NSAID, particularly with no selective joint injections, other agents. And if the mechanism is just reduction of pain, other adjunctive medicines may worsen this, and I think that information would be very important in the design of any REMS as to what would be the allowable or not allowable therapy.

But with respect to the second, it seems that we're focusing on radiographs as opposed to patients' symptoms. And it seems that when you have an effective analgesia, some of the symptoms that may be associated with the arthritis get attenuated, which you have good analgesia. What I would be interested in is what happens when you

stop tanezumab in those people who have a radiographic change. This is a relatively short-term measure. Do they have more pain than they started with, and do they have more pain in other joints because there's been pressure?

So while total joint replacement may wait several years, increased pain, however, may occur very soon. And I think if there are data available to say what was the outcome at the discontinuation of tanezumab, that would be very helpful in evaluating the potential REMS. That's all for my comment.

DR. SUAREZ-ALMAZOR: Thank you.

May I remind the panel members, if you have already made your comment, if you could lower your hand after, because some of them are still raised up, and I don't know if you have another comment or not. So please remember to lower after you have spoken.

Dr. Meisel?

DR. MEISEL: Thank you. Steve Meisel from Fairview in Minneapolis; a couple of thoughts here.

There's been some discussion and lack of clarity as to whether this joint destruction is related to increased function -- so it comes at that Catch-22 cycle that Mr. O'Brien referred to before -- or whether it's chemical.

It seems to me that hasn't been well differentiated, but as I think about Study 1058, the efficacy between NSAIDs and this drug, there were no differences. But the risk of destructive arthropathy was clearly higher with tanezumab, which suggests to me that this is a chemical issue more than it is a functional issue.

Knowing that the chemical, when you inject it, is going to sit around for a while, the long-term effect of that I think is something we shouldn't dismiss. Even if you stop it, the chemical is going to be there for a while, chemical being the drug itself.

The fact that there is, at least, some impact on healthy joints higher than what otherwise would be predicted, I don't think this has been that well characterized, but I think we ought to be

thinking about the frame of reference, that this destructive arthropathy is not totally because of improved function, but it's because there's something pathophysiological that's going on with this drug itself in terms of its mechanism of action. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Nelson?

DR. NELSON: Thank you. It's Lewis Nelson from Rutgers Jersey Medical School in Newark. I appreciate the presentations and all of the questions. I think we've been talking about this drug on and off for about a decade now, and the point in this is not more long-term data, as has been already commented on.

I mean, we could go back and look at that respectively, but it probably should have been looked at in an ongoing fashion by the sponsor. Many people received these drugs in the initial trials before 2015, and they can certainly look back and see what's happened to those people, to those patients, subsequently, or those subjects.

This is especially true, given that the

Kaplan-Meier curves really do not seem to flatten. And even if they want to be interpreted as flattening, it's certainly not clear that there's not a secondary later developing adverse effect that we would probably be able to better predict if we had an understanding of the biological plausibility of risk, and benefit as well.

There does remain, I think, just too many unknowns at this point. As has been mentioned, we don't know what happens when you stop the drug, whether it's for-cause or just because it's not effective. But certainly the for-cause one is probably most concerning and something we'll be talking about a little bit later. But the lack of understanding of the mechanisms of joint destruction and whether it regresses or progresses does have a lot of implications downstream for the continued use of the drug. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Horton?

DR. HORTON: Yes. Dan Horton from Rutgers University in New Brunswick, New Jersey. In terms of point A, one of the things that struck me about

Study 1058 was that MRIs were routinely collected in follow-up I guess for those with more advanced osteoarthritis, but they were not always interpreted. I think it was triggered by changes on plain radiographs.

I guess it's a question of whether -- given that the FDA presentation suggested the MRI is more sensitive, as we see in many other joint conditions, even in the time period that was studied -- the risks of arthropathy, even mild arthropathy, or early progression was underestimated by not reviewing all the MRIs obtained.

I'll also just comment with regard to the hypothesis of the improved benefit leading to worse joint progression, that it would have been nice to show even data, again, from the study population that those who got more benefit were also at higher risk for developing RPOA, and I don't recall seeing those data. Thank you. That's all.

DR. SUAREZ-ALMAZOR: Okay. I don't see any more hands raised.

Is there any more discussion on the topic at all?

DR. VERBURG: This is Ken Verburg from Pfizer. We have some information about the interpretation of MRIs from Study 1058, if that would be useful to see.

I also want to point out and remind the committee that Dr. West yesterday talked about, or showed you, a slide that examined the progression after treatment was stopped, and we could show that slide again, too, if that would be useful.

DR. SUAREZ-ALMAZOR: Okay. Don't show the slide you've already shown, but if you want to make a comment about the interpretation of the MRI, keep it short, under one minute, so we can move on.

DR. VERBURG: Okay.

Dr. West, you could go to the screening MRI assessment first.

DR. WEST: Thank you.

DR. SUAREZ-ALMAZOR: One minute, please.

DR. WEST: Yes. We did look for differences in the findings on MRIs, looking at bone marrow

edema; cartilage morphology; meniscus morphology, presence of root tears; and synovitis, and we did not find anything that was predictive and identified patients who were more at risk.

When looking at post-baseline findings, FDA, you correctly point out, made mention of bone marrow edema being present on patients with RPOA events, and that is correct. But we did some analyses looking at matched controls in which we matched for gender, treatment, number of subcutaneous doses, and KL grade, and we also see increases in those patients during the timing of doses and, again, not specific to treatment.

So we don't think that the presence of bone marrow edema is predictive, as that's commonly seen in patients with OA. As different flares increase, you might see increases in bone marrow edema. So we're, again, indicating in our REMS that if there are any lesions, increases in pain, disproportionate pain to x-ray, any equivocal findings, our recommendation is that MRI should be used to evaluate the joint more fully. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Thank you.

Anymore questions or comments?

(No response.)

DR. SUAREZ-ALMAZOR: No? Okay. I will summarize what has been discussed.

There is general appreciation of the thorough analysis of the data that was performed by Pfizer and the FDA, and there's also recognition of the difficulty of adequately evaluating low-rate adverse events, however, there were many concerns brought up by the panel.

First, the drug might be used for many years, but the longer study just had 56 weeks. There's no evidence on cumulative effects with longer use, but there are some signals within the short periods of time that were covered in the trials that the risk seems to increase during follow-up, even with the short duration.

There were also concerns that follow-up after discontinuation was too short. The effects on other joints were considered to be important, including possibly increased pain for which no data

was presented and also future joint replacement in these joints with little damage to start with; and no data on whether subsequent surgery on joints with rapid progressive arthropathy would be more challenging.

There was a discrepancy in reading the x-rays that also rendered interpretation of the data challenging. And finally, several committee members had comments on the lack of knowledge about etiology that raised concerns about long-term effects.

The biomechanical hypothesis does not explain why there is no joint damage with the use of other analgesics alone. Also, if this hypothesis were to be true, that would raise concerns about the use of concomitant medications that could also worsen the joint damage.

Okay. Any more comments or questions on my summary?

(No response.)

DR. SUAREZ-ALMAZOR: No? Okay. We will then move to question 2. The discussion point is

as follows.

Considering the risk mitigation strategies using the post-2015 studies with tanezumab, A, discuss whether these strategies are effective in mitigating the risk of destructive arthropathy;

B, discuss whether the proposed risk mitigation measures are adequate to identify tanezumab-mediated adverse events on the joint prior to radiographic evidence of joint damage;

C, discuss whether these strategies can successfully be implemented in routine clinical use as part of a REMS; and

D, discuss whether there are additional risk mitigation components that could be added to prevent or reduce the incidence of structural joint damage.

First, let me ask if there are any questions about the wording of question number 2?

(No response.)

DR. SUAREZ-ALMAZOR: No clarifications needed? Okay. We will move on to the discussion then.

For these questions, there are four different points. We will discuss each of these points separately, so we'll start with A, discuss whether these strategies are effective in mitigating the risk of destructive arthropathy.

DR. CHOI: Dr. Suarez-Almazor, can you please check the textbox and let me know if you are receiving my messages?

DR. SUAREZ-ALMAZOR: Oh, okay. Sorry. I was reading, and I -- okay.

Dr. Dunn from the FDA would like to comment.

DR. S. DUNN: Hi. This is Somya Dunn from the Division of Risk Management. I apologize to take us back to question 1 just for a second. I just wanted to clarify something from what the sponsor had brought up about the REMS program.

There was very limited data, according to my understanding from the clinical review team, regarding MRI. MRI was not used in the clinical program to evaluate or mitigate RPOA, and the amounts of information that came through from the clinical data was very limited. And although the

clinical team has considered it as a possibility for something that might be more sensitive or specific for RPOA, it just wasn't something that was evaluated.

Furthermore, it was not proposed in the REMS at all and incorporated in the REMS program at all. We did note that the sponsor included some MRI recommendations in their REMS slides for the AC, however, we haven't received any materials or any requests, or amendments, or proposals that incorporate MRI.

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

Okay. We will move then to discussion of question 2, point A.

Dr. Cheng?

DR. CHENG: Yes, thank you. As I alluded to yesterday in my comments, I believe, as I understand the REMS program proposed by the applicant and described by Dr. Hicks, it's going to track and screen for the developments of the adverse effects, but it does not mitigate the adverse effects.

The adverse effects of the joint destruction subchondral insufficiency fracture and osteonecrosis, while no studies have been done on the natural history of those in this trial, I can tell you that those entities, those are irreversible changes in the chondral structure of the knee or hip, or whichever the affected joint is.

But these are irreversible changes, and as I heard someone say -- I think it was Dr. Pokrovnichka yesterday -- that once these changes occur, the statement was made, "You'd have a joint replacement around the corner," well, I don't know if it's around the corner, but it likely is inevitable if you want pain relief and you live long enough.

So I do not think -- it would be important to mitigate these adverse effects, but, unfortunately, the REMS program, as designed, doesn't do that. So that then raises the question of how do you do that? That's a legitimate question, and perhaps the applicant is doing its

best as can be done. That's part B, C, and D, I believe, of these questions.

As was just mentioned a few minutes ago, MRI examination in general will detect chondral damage sooner than radiographs because the radiographs are dependent upon the positioning of weight-bearing of the joint being imaged.

Also, the chondral damage may occur in different parts of the joint surface. It may not always be in profile with the routine standard inter-posterior and lateral views. So that's why things like the Rosenberg view or a PA radiograph with weight bearing and 45-degree knee flexion is sometimes used because it's more sensitive for detecting and demonstrating the chondral loss that may occur.

There is standard MRI examination using the mood sensitive or T2 star techniques may be helpful. In addition, there are some research sequences that can be used, but those are not in routine clinical practice, so it's not practical for a REMS program. But the MRI, in general, will

look at the three-dimensional structure of the joint much better than a radiograph would do. But still, it's looking for irreversible damage, or it's looking for damage, structural damage, to the joint. And once that happens, it is irreversible.

The one situation where it may not be irreversible is in osteonecrosis. When you have a very small lesion or infarct in the bone, it may spontaneously resolve. We have reported that. But that's for classical osteonecrosis, like related to steroid usage, which is a little bit different than, I believe, that's being reported in these patients. We didn't see images, so I can't say that with certainty, but that's my understanding.

So in these patients when there's subchondral bone loss, or subchondral fracture, or chondral damage, those changes are irreversible, and we have to remember that. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I think the REMS aim to mitigate risk by either selecting a population that is not at risk or

stopping at first symptoms, or stopping at progressing to reverse. And in this particular case, I think that selecting a population at no risk is not possible because we don't know the risk factors of who is going to develop the condition other than using NSAIDs.

Stopping at first symptoms cannot be done because for most patients, the processes are symptomatic or silent. And when we stop at radiographic deterioration, as Dr. Cheng said, it's too late because it is not reversible.

So I think the sponsor is proposing as much as they can do, but I don't see how this is going to mitigate the risk. And I think we need to keep in mind that increasing awareness is not mitigating the risk. Reducing the number of patients that are going to use the drug without identifying a group at a lower risk is not mitigating the risk. Identifying the damage is not mitigating the risk, and of course stopping using it if it does not work is not risk mitigation.

So despite I think a very comprehensive plan

that the sponsor is proposing, I don't see how it is going to successfully reduce the risk of destructive arthropathy. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Dr. Singh?

DR. SINGH: Jasvinder Singh, University of Alabama at Birmingham. I won't repeat many of the points just made by our colleagues. I'll just maybe add a couple other things that are concerns.

Diagnosing destructive arthropathy is perhaps possible with several caveats that go to point B, C, and D that were discussed; that I agree with the two speakers before me that diagnosing destructive arthropathy, RPOA-1 or RPOA-2, only leads to a diagnosis. It does not reduce the risk, it does not moderate the risk, and it does not stop perhaps the risk of further progression, which can only be known with long-term studies.

Also, I think despite the best efforts of the sponsor, made within the context of the study, we do not know of pre-RPOA-1 lesions, and perhaps RPOA-1 is pre-RPOA-2. But I think a lot is already lost to RPOA-1, because of the subsequent impact of

that or the natural history of that that is also not known very well.

So in the absence of known clinical risk factors, in the absence of clear knowledge whether MRI is a more sensitive tool to detect this ahead of [indiscernible] of radiographs, and in the absence of a definition and an understanding of a pre-RPOA-1 lesion, I'm not sure it's possible to mitigate destructive arthropathy. Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Dr. Calis?

DR. CALIS: Yes. Thank you. So needless to say, I think we're all kind of dwelling on the same issues. Question 2 is obviously the key to our discussion today. I think we're sort of reflecting on it a lot because of the fact that I think the REMS program addresses just a portion of what it's really meant to address, and I think that's what some of the speakers before me have said.

So really, other than missing a great opportunity for long-term follow-up with the research participants, which is a major, major

limitation, the sponsor's kind of done really an admirable job in trying to characterize the destructive arthropathy. And like with many other adverse events, sometimes, unfortunately, it's not possible to elucidate the precise mechanisms of these serious adverse events and all the key risk factors that can inform risk mitigation, which is really the key here.

So the proposed REMS would certainly, to my mind, successfully limit indiscriminate use of tanezumab, but my concern would be that we'd still have to be cautious that use in a real-world setting could expose patients to greater risk than that seen in the controlled clinical trials.

So the overall concern is not with risk evaluation; I think the REMS will really inform clinical safety. My concern is for the patients that will continue to receive this drug long term and my lack of confidence in the REMS program in terms of the risk mitigation. So I think that that's really central to our discussion today. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Kulldorff?

DR. KULLDORFF: Thank you. This is Martin Kulldorff. I agree with Dr. Hernandez-Diaz and others, that for the REMS to work, either two things have to be there. Either we have to be able to identify ahead of time those that would have developed the joint adverse reactions, and I have not seen evidence that that can be done; or it has to be monitored closely so that we quickly can find when somebody's developing that before there is damage, and I haven't seen evidence for that either.

DR. SUAREZ-ALMAZOR: Thank you.

Anyone else? No more questions?

DR. VERBURG: This is Ken Verburg from Pfizer. Could I have --

DR. SUAREZ-ALMAZOR: Yes, just a second. There are a couple of panel members that --

DR. VERBURG: Thank you.

DR. SUAREZ-ALMAZOR: -- have questions.

Mr. O'Brien, your hand is up. I don't know if you have another comment or that's from before.

Mr. O'Brien?

MR. O'BRIEN: Hello? Can you hear me?

DR. SUAREZ-ALMAZOR: Yes. Go ahead.

MR. O'BRIEN: Joe O'Brien. I just wanted to say, in following up what I had said in the first discussion, I agree with everything that's been said in terms of it seems to be, from a patient perspective, that the strategy that was used in regard to A, it reduced down the number of people but it didn't mitigate the risk.

My concern is that in looking at the REMS, again, if the sponsor truly believes that this is not a chemical issue, that it is a function, that puts it on the part of the patients. So we have within the REMS telling them that they cannot take NSAIDs, and now we're going to tell them that they can't function. But that's not addressed in the REMS whatsoever.

So I become very concerned in terms of the capability, going down to D. That would have to be added, and I don't know how that's practical to tell them because that's the very reason why

they're taking the drug in the first place.

DR. SUAREZ-ALMAZOR: Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I think the major and most important issues were well covered already and I won't mention them. One that was, at first, very important to me was the issue of the patient's preference and the willingness of the patient to take on the level of risk.

You know, informed patient consent, the REMS program is supposed to be the cornerstone of that for entry, high-risk drugs. For people who are in pain today, and if other drugs have failed and their doctor is recommending or suggesting this product, they may not feel that a 1 or a 3 percent possible increase in total knee replacement is a big risk, but it is, particularly over the tens of thousands of people that might be offered this drug.

While patient preference information is important, I don't think it's the keystone to making a decision, or there'd be little use for the FDA. Patient preference for antibiotics, for

example, for common flu, is quite high, yet it's inappropriate. So I just wanted to add that potentially minor point of view. Thanks.

DR. SUAREZ-ALMAZOR: Okay.

Dr. Meisel?

DR. MEISEL: Thank you. Steve Meisel from Fairview in Minneapolis. I agree with most of the previous comments, particularly those of Dr. Cheng. One element of the proposed REMS I think would be helpful as a risk mitigation strategy, although I don't think it's practical, is to limit the amount of NSAIDs.

Now, we know that chronic use of NSAIDs in combination with tanezumab increases the risk, and if we tell people not to use the NSAIDs, that's going to mitigate that increased risk. That said, I'm not sure how practical that is on a real-life basis because we know that people will continue to have pain and issues even if they take this tanezumab. And we can tell them to limit their use to one tablet every 5 days or whatever; that's not terribly practical in the real world. But if that

were to be applied and operationalized in a way that people adhere to that, that is one minor element of the REMS program that I think could have a risk mitigation success. Thank you.

DR. SUAREZ-ALMAZOR: Okay. I see a couple of hands that are still raised. I don't know if anyone has an additional comment to add, or if not, please lower your hand.

Dr. Cheng, do you have another comment?

DR. CHENG: Yes. It's a new comment. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Go ahead.

DR. CHENG: I just wanted to put in perspective this risk of the joint destruction. Most of us are talking about the index joint or the targeted joint. But I think the greater risk, really, is the non-index joint because most of these patients do have other articular symptoms. So those that are at the higher KL grade, obviously, the sponsor has shown they're at higher risk for problems.

So the real risk, in my opinion, has to do

with the non-indexed joints because if you're willing to take -- I mean, after all, as people have said, you can take a steroid shot. That has risk, too, for joint destruction. We know that biologically and in the laboratory. Yet, people do this all the time, and it's widely acceptable as standard treatment.

Yet, here we're concerned about the risk with this drug is. You may feel that's unfair. Yet, the storage has a local treatment. This is a systemic treatment, and we're talking about risk to other joints that maybe isn't warranted or we'd rather not see. So that's the difference here. Thank you.

DR. SUAREZ-ALMAZOR: Okay.

Dr. Pisetsky?

(No response.)

DR. SUAREZ-ALMAZOR: Dr. Pisetsky, do you have your hand raised?

(No response.)

DR. SUAREZ-ALMAZOR: No?

Okay. I will let Pfizer respond to some of

these comments, just one minute, no slides, no new data.

DR. VERBURG: Thank you. Let's go directly to Dr. Wilkins, who will provide some additional detail on the REMS.

DR. WILKINS: Hi. My name is Jamie Wilkins with worldwide safety at Pfizer. We wanted to make one clarification about REMS for the committee; that while REMS are intended to mitigate a risk, and while many REMS do have interventions that may prevent a risk from occurring, there are a significant proportion of approved REMS that are designed to mitigate via other methods.

This could include interventions that can prevent a risk from becoming worse should it actually occur, or a REMS can monitor for a risk so that prescribers can have a patient-specific conversation with their patients regarding the benefit-risk of actually continuing therapy with the product.

There are several FDA approved REMS and programs that achieve such goals and mitigate

serious issues such as PML, visual acuity loss, or valvular heart disease, that do not actually prevent these risks from occurring but mitigate through the other important goals that were just mentioned. So that was a clarification we wanted to make for the committee. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Thank you.

Dr. Pisetsky?

DR. PISETSKY: Yes. The issue I wanted to bring up was the dose response, which I think is quite striking. There really is a difference between 2.5 and 5 milligrams, yet you would expect in a population of patients, there would be a distribution of weight and that some of the risk could be weight-based in terms of milligrams per kilogram with dosing.

We haven't seen discussion of that, and I was just wondering whether there's any potential of mitigating risk by doing weight-based adjustment of dosing.

DR. SUAREZ-ALMAZOR: Okay. Thank you.

DR. VERBURG: I can respond to that.

DR. SUAREZ-ALMAZOR: Dr. Cheng, your hand is raised.

Okay. Go ahead, very quickly.

DR. CHENG: I'm sorry.

DR. VERBURG: Yes. So the question was really regarding, I believe, exposures on an individual patient basis at the dose of 2.5 and how much overlap there is with the 5-milligram dose. I'd like to go to Dr. Scott Marshall real quickly for an explanation and description of those.

DR. SUAREZ-ALMAZOR: No more than one minute, please; no more than one minute.

DR. S. MARSHALL: Sure.

Thank you, Dr. Verburg.

Yes, we have studied the pharmacokinetics of tanezumab extensively across the program, and like all monoclonal antibodies, the variability in the PK is low to moderate, a 30 percent coefficient of variation. And that means that there's very little overlap in the exposures between 2.5 milligrams and 5 milligrams. So in essence, the two doses are fairly distinct with respect to the exposure.

Thank you.

DR. SUAREZ-ALMAZOR: Okay.

Dr. Pisetsky, your hand is raised. Do you have another comment?

DR. PISETSKY: It's just that another monoclonal -- there's been a discussion of the impact of obesity, for example, on dosing. And one might expect in the patient population with osteoarthritis, there would be a certain amount of obesity, and that was the reference to my question about weight.

DR. SUAREZ-ALMAZOR: Okay. Thank you.

If there are no more comments, I'll just summarize what was discussed. The sponsor, it was felt, had done a thorough job trying to characterize arthropathy, but unfortunately there is no sufficient data to better inform the REMS. One of the approaches that was felt to be useful is limiting NSAIDs, but that was about it with respect to risk factors.

There was a concern that the REMS screens for arthropathy but does not mitigate the risk, as

once the lesions are detected, they are irreversible. Many lesions are initially asymptomatic, so discontinuing treatment when symptoms increase is not likely to be an adequate enough measure.

There was a concern about the use of standard x-rays alone, as the views that are normally used may not be sensitive enough to detect early changes. It is not possible with current evidence to identify those at risk before they start receiving treatment or to identify lesions early enough so they can be reversible. There was also some concern about information provided to patients on the REMS in relation to the risks and also in relation to patient preferences.

Okay. No comments.

We will then move to question 2B. Discuss whether the proposed risk mitigation measures are adequate to identify tanezumab-mediated adverse events on the joint prior to radiographic evidence of joint damage. We have discussed some of this, but if someone wants to address it more

specifically, please raise your hand.

(No response.)

DR. SUAREZ-ALMAZOR: There was a comment as to whether symptoms could be used to identify early damage, and it was felt that this is probably insufficient.

Does anyone have any comments about that?

(No response.)

DR. SUAREZ-ALMAZOR: No?

(No response.)

DR. SUAREZ-ALMAZOR: Okay. So we will move to point C. Discuss whether these strategies can successfully be implemented in routine clinical use as part of a REMS?

There were some comments earlier as to whether x-rays alone would be sufficient and the need for MRIs, which would not be easy to implement and has not been proposed as part of the regular program.

Dr. Nelson?

DR. NELSON: Yes. Thank you. I have some serious concerns about the ability of a REMS, the

proposed REMS in particular, to be effective to reach its stated goal. Given the attentiveness to the adverse effects within the study population, and then the known limitations of even ironclad REMS that we currently have, not having the intended outcome that we can anticipate, I don't know how we're going to really be able to predict the real-world outcome.

It will certainly be less optimal than it was in the research world, but will it be sufficient to screen, identify risks, and actually act in a way to positively impact that risk?

Requiring low sensitivity testing, meaning x-rays, and not very expensive and difficult to obtain MRIs at defined intervals, or even if done for-cause, seems a little less like risk mitigation and more like damage control. We really won't have any ability to impact, it appears at least, the ongoing effects that the patient is having. So I am concerned, in addition, that we don't have an adequate system to assure that all of the steps in the REMS will be accomplished as stated.

There's a lot to be said for educating patients, and nobody would argue against doing that, but we don't really know what happens behind closed doors. We don't know what happens when somebody goes to a pharmacy or goes to get an x-ray.

There are just too many potentials for missteps. And again, these ironclad REMS that have really put very strict boundaries, strict guard rails, on processes have failed., and I think this one is a little bit looser, certainly, than most of those have been, and still are.

When you think about even the radiology-related issues, how consistent are radiologists' interpretation of real world? I mean, we've spoken a bit about this already, but we're talking about millimeter changes in joint width. I know that the sponsor and others will provide help in getting this done, as have other sponsors of REMS in the past.

Often these requests or supports have been rejected, or ignored, or even, in a very benign

way, just not followed. But remember, we will not have presumably musculoskeletal radiologists reading most of these actually, but rather more general radiologists. We may not have technologists performing the x-rays who are highly skilled and understand the details of how a film has to be performed, as Dr. Cheng commented earlier about the specifics of weight bearing, and angles, and things like that.

We haven't heard that these have really been studied in a real-world setting and whether or not the sensitivity/specificity that they have for these studies, for these findings, in the research world will apply out in the real world. So I think there are a lot of concerns.

Then there's the overriding concern about indications risk, as we see with many drugs that are approved, and how this is going to impact people who might have different forms of this disease or different diseases altogether and wind up getting this drug, as we know happens with many others. There's really no guard rail on that

happening either, based on the REMS. And even in a REMS that have those guard rails in place, there's still indications risk.

So again, I've been involved with these REMS programs for a number of years, as has many people on this call. And I think while they're good, they just have so many holes and so many limitations, and they're almost unenforceable in most conditions, that I do have some concerns that this will not be very effective when it's put out in the real world.

DR. SUAREZ-ALMAZOR: Dr. Cheng?

DR. CHENG: Thank you. As the sponsor is already doing as much as they reasonably can, and we on the committee have not been able to provide substantial improvements to the proposed REMS, I guess I don't think the modest benefit outweighs the risks. So what's needed is more demonstrated evidence of higher efficacy. So this last question is basically getting at the approval question, I think is what the FDA is asking us in a kind of indirect way.

I concur with the sponsor's contention that there's an unmet need for efficacious treatment of osteoarthritis. And more so in both my own practice and in the testimonies presented that we heard yesterday, I really hear the plea from patients with chronic arthritis pain looking for relief.

Unfortunately, however, this drug, tanezumab, does not fulfill this need. As it has a similar clinical efficacy and is clinically comparable to existing therapies, it's really no better than taking aspirin or an ibuprofen, and does not avoid or delay total joint arthroplasty, as imperfect a metric that is; that I just stated earlier it's not better than an anti-inflammatory; in fact, in some ways it might be worse, as some of the data has shown. It only offers another option for people but has a higher risk profile, which is what some of the slides showed.

So why would we approve a drug treatment for osteoarthritis that's minimally better than placebo; no better than existing therapies like

aspirin and anti-inflammatories; has a worse risk profile than placebo and existing therapies, to the point that we're tussling with this REMS program, which more accurately, in my opinion, is a postmarketing surveillance program; and it poses risks to non-target joints, resulting in irreversible damage, and I'm sure it's going to be costly. Furthermore, it's a new class of therapy, which I stated we should be cautious about because we don't know the longer term safety profile in the larger real world.

So this treatment, one could say, is targeting those patients that cannot take an anti-inflammatory, like the patient Robert that we heard about yesterday. But there are other options; non-pharmacologic, for example. There is radiofrequency ablation. There's embolization and the old standby of steroid injections.

So while I would support approval of a drug if the efficacy was strong enough to be considered a game changer, this unfortunately is not a game-changer drug. We should keep in mind that

this is not the only chance for tanezumab to be approved for usage. It is being studied as a non-opioid analgesic for low-back pain, metastatic bone disease, and perhaps other indications I'm unaware of.

So I conclude that we should be careful and would not approve this drug based on its current safety and efficacy profile. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Dr. Chen, we are not supposed to discuss our vote before the vote, actually. We were discussing point C, which is whether these strategies can be successfully implemented in routine clinical use. So I don't know if you had any comments about that particular question, rather than on the overall vote.

DR. CHENG: And I'm sorry. I thought that's what the broad collection was. I apologize.

DR. SUAREZ-ALMAZOR: Yes, implementation in routine clinical use.

Okay. So no comments on routine clinical use? No?

DR. CHENG: No more comments.

DR. SUAREZ-ALMAZOR: Okay. Thank you.

Dr. Griffin?

DR. GRIFFIN: Marie Griffin, Nashville, Tennessee. I was just going to reiterate again, I think the REMS, you think it's a good idea that people are getting education every 8 weeks about not using NSAIDs. We see a similar thing with warfarin. People go in for their PT once a month and get educated about what they're not supposed to use, but, again, I remain concerned that people still use NSAIDs, and that this combination is really dangerous, and it makes this a much worse risk.

So I think education about NSAIDs will not be sufficient to prevent their use. That's all. Thank you.

DR. SUAREZ-ALMAZOR: Yes. And if I may make a comment, I agree with that, especially, because NSAIDs are over the counter. and very often patients are not clear as to what is an NSAID and what might be just an analgesic such as acetaminophen.

Dr. Katz?

DR. KATZ: Thank you. Lee Katz, Yale University. I guess as a musculoskeletal radiologist, I've been listening, and I think I probably should make a few comments. I would have a tendency to agree with the other speakers about having non-musculoskeletal radiologists monitoring the progression adequately. And more importantly, the training of the technologists taking the imaging is very important.

In addition, a comment was made about MRI I guess by Dr. West, and I think I should say a few things certainly about bone marrow edema, which is a difficult topic in itself in terms of its presence, the initiating factor, how long it's been there, et cetera.

But usually we don't see bone marrow edema associated with osteoarthritis unless there's been full thickness articular cartilage loss, of which usually joint fluid then is extending into the subchondral bone, or if overuse, we will see edema. But other issues, including subchondral

insufficiency fracture and osteonecrosis, are other possibilities.

I think more work would probably need to be done associated with rapidly progressive osteoarthritis in bone marrow edema; but again, I don't think that would be mitigation following the diagnosis.

I guess finally, there's one other comment. Again from some of the sponsor's presentation, they talked about articular cartilage loss and meniscal damage. I think it's interesting to point out that we need to recognize that with osteoarthritis, we're talking essentially about articular cartilage disease, but menisci are also a form of cartilage. It's fibrocartilage. I'm not sure whether the meniscal damage is due to extrusion from progression of osteoarthritis or, in fact, could there be influences on the cartilage of the menisci from the sponsor's drug. Thank you very much.

DR. SUAREZ-ALMAZOR: Okay. I don't think there are any more questions, so let me summarize, and I'm summarizing on point C, routine clinical

use. There were some concerns about the ability of the proposed REMS to be implemented.

DR. CHOI: Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Yes?

DR. CHOI: I'm sorry. It looks like we have one more hand.

DR. SUAREZ-ALMAZOR: Yes.

Dr. Pisetsky, please go ahead.

DR. PISETSKY: Yes. I think one issue that has not been brought up is who takes care of patients with osteoarthritis in terms of implementing any strategies. There care is variably divided among general internists; rheumatologists; orthopedic surgeons. I think implementing any kind of REMS really just has to take into account who's caring for the patients and what their relative expertise is in; disease managers, also radiological assessment, and in the real world, rheumatologists are also reading joint x-rays. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Thank you.

Yes, there were some concerns about the

ability of the proposed REMS to be implemented. It was mentioned that other --

DR. CHOI: Dr. Almazor, the sponsor would like to provide some comments [inaudible – audio gap].

DR. SUAREZ-ALMAZOR: Okay.

DR. VERBURG: Sure. Actually, I'm going to turn this over to Dr. Schnitzer to just briefly talk about the trade-off of the benefits here and [inaudible – audio gap] brought up earlier.

Dr. Schnitzer?

(No response.)

DR. VERBURG: You may be on mute.

DR. SUAREZ-ALMAZOR: Yes. And Dr. Schnitzer, please --

DR. SCHNITZER: Sorry --

DR. SUAREZ-ALMAZOR: Yes. Dr. Schnitzer, please keep it short to one minute only. Okay? Thank you.

DR. SCHNITZER: Yes.

Let me talk about this critical issue of benefit-risk and how it's best assessed, and by

whom. There's a general consensus today that this is best assessed in the context of shared decision making. This was defined by Dr. Marshall in her presentation yesterday, nicely, the collaborative decision process considering scientific evidence and patient values and preference.

"The role of the FDA, with the help of the sponsor and this committee, is to ensure the integrity of the adequacy of this scientific evidence. Engagement with the patient is the province of the clinician, educated and trained to assess if a particular treatment is appropriate, given the patient's clinical status, their values, and preferences."

Now, I sort of feel, whether due to hubris or leftover paternalism, regulatory bodies have often felt that they should be making these decisions in the absence of the patients. In today's world, that's not really proper nor desirable.

I would encourage the committee to endeavor to make sure that the data are adequately clarified

and scientifically rigorous, and to trust the clinicians and patients have the wisdom and insight that will allow for the best and the proper use of this important new treatment option. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Any more comments before I continue summarizing what was said? I don't see any hands raised.

(No response.)

DR. SUAREZ-ALMAZOR: No?

(No response.)

DR. SUAREZ-ALMAZOR: Okay. So I'll summarize again. There were concerns about the ability of the proposed REMS to be implemented in clinical practice. It was mentioned that other tighter REMS have not been as successful, and these were felt to be a little looser.

There was general concern about radiologists' evaluation of progression in the real world, as there's no data presented on the real world studying evaluations. There were concerns about not only these radiologists being able to measure joint space narrowing far away, but also

other lesions, and even meniscal lesions.

There is no guard rail in the REMS for inappropriate indications, and there was a concern about the use of concomitant NSAIDs, and that perhaps education alone may not be enough, and this would be a very deleterious problem if patients were to use NSAIDs at the same time as they receive tanezumab.

It was also felt that there are many different specialties that take care of patients with OA, and that the REMS should address these practice patterns that vary across clinical settings.

Any comments or additions? No?

(No response.)

DR. SUAREZ-ALMAZOR: Okay. We can then move to D. Discuss whether there are additional risk mitigation components that could be added to prevent or reduce the incidence of structural joint damage.

Does anyone have any comments on what components could be added?

Dr. Richards?

DR. RICHARDS: Good morning. John Richards from the VA in Pittsburgh. I think we keep coming back to the lack of long-term data, and I think without knowing that, it limits our ability to come up with additional risk mitigation strategies.

I think if we had longer term data and knew if the drug was stopped at time X, and there was no further progression, theoretically you could enroll patients who had significant OA of one joint and their other weight-bearing joints did not have OA, and then you monitored those joints, potentially, you could mitigate the risk of joint damage there.

The other thing is that I think the design of the study really didn't look at activity of the patient. The WOMAC functional index is really looking at activities of daily living and not recreational activities, which I think the sponsor was alluding to, and may be responsible for joint damage. So I think those things kind of limit us from coming up with different strategies that may aid in risk mitigation. Thank you.

DR. SUAREZ-ALMAZOR: Okay.

Dr. Pisetsky, I believe --

DR. PISETSKY: No.

DR. SUAREZ-ALMAZOR: No. Okay.

Dr. Honczarenko?

DR. HONCZARENKO: Thank you. Marek Honczarenko. I would like to add that this is an incredible opportunity, considering the incidence of adverse events, to really look into the opportunity for us to advance the whole field of research in osteoarthritis and try to identify either complementary or predictive diagnostics of adverse events.

You know, with these incidence rates, we can hope for having potential biomarkers with very high predictive correlation. I'm obviously aware of the sponsor's work on the serum and other imaging biomarkers.

For heterogeneous disease like osteoarthritis, we have this opportunity here to identify in the postmarketing setting the biomarkers based on the genetic polymorphism, and I

believe that this could be something which can be relatively easily implemented and correlated with the rest of the components of the REMS and actually advance the field as a whole; because, obviously, unfortunately, for the whole field of rheumatology, it is very disappointing [indiscernible] that we are not able to come up with any predictive biomarkers.

And here, we already have a science that could help; and not only that, but essentially in the long term could help to identify the patients who are at higher risk of total joint replacement and potentially use this science to prevent total joint replacement or delay total joint replacement in these patients. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I recognize the benefits of REMS for education and awareness after the discussion we had today, but I am still concerned about the implementation when the marketing aspects come in, and it is presented as an NSAID or not for everyone. Not to be

paternalistic, but I think that is going to be interpreted as, if NSAIDs are not controlling your pain, this drug is going to control your pain. Well, we have seen in the clinical trials that there was a period that the probability of the benefit was the same for NSAIDs and the new drug.

But thinking about these additional risk mitigation components, I wonder if in their awareness and education, the indication for this treatment would be restricted to those patients for whom NSAIDs are contraindicated; not that the NSAIDs are not working only, but they cannot take NSAIDs. Perhaps these are GI [indiscernible] conversations in the past or something like that.

I think that will further restrict the group of patients to those that really cannot take NSAIDs and not only based on a promise of efficacy. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Any more comments about additional risk mitigation components?

(No response.)

DR. SUAREZ-ALMAZOR: Okay. Our next question will be the voting question. Before we move ahead, does anyone else have a general comment with respect to question 1 or question 2 that has not been addressed? Now will be the time.

Mr. O'Brien?

MR. O'BRIEN: Yes. I would just like to address the comment that we just heard with Dr. Schneider [sic] as it relates to the REMS, too.

Again, it seems to me that when we're talking about a new class of drugs with the risks that are here, the only two mitigations are really to understand the etiology and whether or not it would be a biological chemical, or whether or not a matter of function in loads, increased loads, that the patient puts on their self as they go forward. Those are the two that have to be addressed, which I don't see either one of them addressed within the REMS.

And yes, it is true, as Dr. Schneider says, that clearly we want shared decision making at the end of the day between the patients and themselves.

I am a patient who has had, is on actually, NSAIDs, both Tylenol, and Advil, and Eliquis, and OxyContin. I've had gabapentin, Celebrex, et cetera. And with each one of them, I have had a shared decision. But yet at the end of the day, 3, 5, 10 years later, we find out that in fact the risks that we thought, are more than we thought, and we're always backtracking on it.

Here, we're talking about a particular new case of drug that has the potential, systemically, to affect a patient later on. There's no doubt about it. I have an 89-year-old mother that can't take shots anymore, who shoulders the shot and just doesn't want a surgery at this point in time. There's nothing for her for that.

Clearly, we want an issue, and rightfully so, we need something that is non-addictive pain medication. But we can't be putting on additional risk to patients that we don't understand, because we're only going to be dealing with it five years later. And I just don't see how these risks -- if they don't address those two issues, then we really

can't identify it going forward.

DR. SUAREZ-ALMAZOR: Dr. Hovinga?

DR. HOVINGA: Collin Hovinga. In looking at the feasibility of the REMS and looking at patients and whatnot, oftentimes the financial aspects of completing obligations are a really important factor.

Will the burden of the tests and other procedures that will need to be done be on the patients? Because of compliant issues, I wanted to know if it has to be covered by insurance or whatnot. Thank you.

DR. SUAREZ-ALMAZOR: Is that a question that you're posing to the sponsor or just a comment?

DR. HOVINGA: I guess either the sponsor, or if there's a patient advocate that's in the mix that can weigh in on that perspective, that has the condition or knows more. Thank you.

DR. SUAREZ-ALMAZOR: Okay. Let's see if any of the patient advocates in the panel would like to respond to that.

Mr. O'Brien?

MR. O'BRIEN: Sorry. I didn't realize my mic was on.

I'm sorry. If you could just rephrase the question. Was it regarding insurance?

DR. HOVINGA: Yes. I guess there are two things, I think, really when you come from a patient's perspective. One, is this going to be perceived as feasible and acceptable for patients to do the follow-up for the REMS? Would adding more items to the REMS be problematic, both from a patient visit perspective, but also financially?

MR. O'BRIEN: Well, I guess if you look -- my answer would be this. Yes, insurance affects a lot of things, but REMS in itself, from the beginning of unfolding a 15-page document that comes with the drug when you get it, I don't know any patients that really take the time to sit there and read it to get all of the warnings.

In a real-world situation, again, depending on where they're getting the drug, there's less than five minutes that are there. And we've found that in many cases that what we hope happens in

terms of a provider, in fact, doesn't happen. So I don't think you can guarantee that or rely on that. Yes, in the most part, everybody's good and they're provided directions or whatever, but in a real world, that happens; so people don't get access to it.

We tell people now, you certainly shouldn't drink alcohol if you take oxycodone, but they do. We have many different warnings that we've provided to them, and education that we've provided, and that we have evidence over and over again that's just not complied with. Patient compliance, it's very little that we can rely upon. We can rely upon their need. That is sure, that's there. But I don't think we can place a whole lot of emphasis, at the end of the day, on patient education or compliance at that level. The more we add on, the less it's likely to happen.

DR. HOVINGA: Thank you.

DR. SUAREZ-ALMAZOR: Thank you.

Dr. Singh?

DR. SINGH: Hi. Jasvinder Singh, University

of Alabama at Birmingham. One of the questions I have, perhaps for Dr. Schnitzer or anybody from the sponsor team, is this issue that was brought up that less pain with this particular product may perhaps lead to more joint loading, which had been noted with some NSAID studies in the early '90s as well.

One of the potential interpretations of that for common masses, for people, and primary care providers may be, A, less pain is not that desirable because it will lead to a total joint replacement sooner, which flies right in the face of CDC recommendations for physical activity, and flies in the face of known association of weight gain with osteoarthritis progression and the known slow-down of the OA progression with weight loss, which are both pretty substantially replicated findings in osteoarthritis epidemiology.

But it also brings in the issue, with a product like this, that physical activity should not go up because it would lead to more joint loading and a sooner TKA. Well, what about the

other consequences of more weight gain that leads to more progression of OA and other unintended consequences, its effect on metabolic syndrome, diabetes, heart disease, hypertension, and also perhaps other consequences of not being active.

So does the sponsor have any thoughts on, even during a REMS program for this medication, if they were to pass on this message, how is that going to be balanced against the unintended consequences of don't load your joint more because pain is less? Thank you.

DR. VERBURG: We'd be happy to respond. Let's go to Dr. Schnitzer for a quick response.

DR. SUAREZ-ALMAZOR: Okay.

Dr. Schnitzer, again, please only one minute for the response.

DR. SCHNITZER: I would just say that I think that increased activity is a desirable end. And then typically what happens in osteoarthritis is if you relieve the pain, people increase their activity, and often back to the same level of pain they were at that was limiting them before, but now

in a much more active state. So instead of walking 2 blocks, they walk 8 blocks.

So all in all, I think this is a good thing. And I would just remind the panel that the incidence of RPOA-2, that's with destructive arthropathy, which RPOA-1 is not, it was 0.4 percent across the entire program, the post-2015 program. This is not a high rate in people who already had major changes to their joints to start with and probably were going to progress to joint replacement soon. Thank you.

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

Okay. I don't see any more hands raised, so let me summarize what was discussed in relation to additional risk mitigation components. Some of the points that were brought up was possibly enrolling patients with osteoarthritis in a single joint to try to avoid damaging the other joints, or unaffected joints, or mitigate damage I should say.

Then there was a fair amount of discussion on patient activities and whether they could have

an impact on the development of RPOA, but not enough information to inform patients on the REMS and what to do. It was just brought up as well that asking patients to engage in activities is good for them, and increasing activity would have a deleterious effect.

There were some comments on providing additional information on NSAIDs and possibly patient selection around the use of NSAIDs as well. There was a comment on the follow-up studies, that they should continue to be done, but using additional information such as the use of biomarkers to try to understand better the adverse event on joints.

There were also some concerns raised around whether patients would be able to adequately and comprehensively read the REMS. The patient education components, they tend to be quite lengthy, and patients don't typically read them. There were also concerns about how much of a burden on patients the additional testing from additional x-rays could cost, and also from an insurance

perspective if they weren't well insured.

Any comments or additions? No discussion?

DR. VERBURG: Dr. Suarez-Almazor, this is Ken Verburg again. I have just one follow-up consideration or question --

DR. SUAREZ-ALMAZOR: Yes --

DR. VERBURG: -- and it's discussion of the suitability of the REMS. And it was --

DR. SUAREZ-ALMAZOR: Dr. Verburg, this is not related to any questions, so we need to move on.

DR. VERBURG: It is related to a question though --

DR. SUAREZ-ALMAZOR: We have let you participate in the discussion. Yes, but no. No. We need to move on to question number 3. Thank you.

Okay. We will now move on to question number 3. This is a voting question, so Dr. Moon Hee Choi will start by providing the instructions for the voting.

DR. CHOI: Dr. Suarez-Almazor, would you be

able to read the question into the record --

DR. SUAREZ-ALMAZOR: Oh, yes.

DR. CHOI: -- and then ask if there is any question.

DR. CHOI: Yes, absolutely. I thought you were going to do the instructions first. I'll read the question first, then.

This is a vote question. Will the REMS proposed by the applicant ensure that the benefits of tanezumab outweigh its risk? If you voted no, comment on what other studies or information would be needed to address the risks of tanezumab and/or modify the risk mitigation program.

Are there any questions on the wording? And again, you're not supposed to say how you're going to be voting, but if you have any questions about question number 3, now is the time, on the wording only.

Dr. Meisel?

DR. MEISEL: Hi. Thank you. Steve Meisel from Fairview; just clarity for this question here. Often we are asked either a supplementary second

question, or whatever, that asks for our advice as to whether or not a drug should be -- we recommend approval or not.

Is this question -- and maybe the question's for the agency -- akin to that? So if we vote, say, no, then we're recommending that the drug not be approved; and if we vote yes, we're recommending that the drug is approved; or are we being asked to think about this in a different way? I just want some clarity about the frame of reference for the question. Thank you.

DR. ROCA: Hi. This is Dr. Roca. I think you should interpret the question just the way it is written; nothing more, nothing less.

DR. SUAREZ-ALMAZOR: Okay. No further questions?

(No response.)

DR. SUAREZ-ALMAZOR: Dr. Choi, do you want to give instructions to the panel?

DR. CHOI: Yes. Thank you.

We will now move voting members to the voting breakout room to vote only. There will be

no discussion in the voting breakout room. Question number 3 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting.

After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will allow that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button. That is the round, circular button in the window that corresponds to your vote; yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed.

Once all voting members have selected their vote, I will announce that the vote is closed. Next, the vote results will all be displayed on the screen. I will read the vote results from the screen into the record.

Next, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to, however, you should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. CHOI: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. CHOI: The voting has closed and is now complete. The vote results will be displayed. I will read the vote totals into the record. The chairperson will go down the list, and each voting

member will state their name and their vote into the record. You can also state the reason why you voted as you did if you want to, however, you should also address any subparts of the voting question, if any.

DR. SUAREZ-ALMAZOR: Thank you. I do not see the list on the screen yet.

DR. CHOI: It will be displayed momentarily, Dr. Suarez-Almazor.

DR. SUAREZ-ALMAZOR: Okay.

(Pause.)

DR. CHOI: For the record, we have 1 yes, 19 no, and zero abstentions.

DR. SUAREZ-ALMAZOR: Thank you. We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote if you wish to, however, please remember to address any of the subparts of the question that correspond to your vote.

We will start with Dr. Singh.

DR. SINGH: Jasvinder Singh, University of

Alabama at Birmingham. My vote is no, and my comment is that there is limited information with regards to early recognition of pre-lesions for the joint destruction and the radiographic adverse event outcomes.

Without the knowledge of that and also unclear aspects of concurrent NSAID use, over-the-counter, topical and oral, and the valued radiographs for detecting lesions prior to destructive lesions, there are some very unique challenges with assessing the risks and whether they outweigh the benefits. And the risk mitigation program, there's an issue with that.

That's the end of my comment. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Oliver?

DR. OLIVER: Alyce Oliver, Medical College of Georgia. I voted no. I do believe that there is not enough information on the systemic effects of the injection, as well as needing long-term data for both active treatment -- so we know that osteoarthritis is a chronic condition, and that it's possible that people could be on this drug for

years. What would be the outcome data for that? Then, there's follow-up imaging on individuals who have stopped the drug, but longer term imaging data to see if there's an effect. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Meisel?

DR. MEISEL: Thank you. Steve Meisel from M Health Fairview in Minneapolis. I also voted no. I think the REMS program is not practical. As Dr. Cheng pointed out, it's not preventive; its diagnostic. It will not be followed very well by patients or providers. The risks of this drug outweigh the relatively modest benefits regardless of the REMS.

I'm kind of reminded of what kind of conversation we would be having if this was a drug for, say, angina, and we had a drug that said, "Well, we could reduce the likelihood that you'd have an anginal attack, but in doing so, you're more likely to have bypass surgery. Yes, if you take nitroglycerin for the anginal attacks, that will help but will further increase the risk of bypass surgery, so cut down on the nitroglycerin

use."

We wouldn't even be having this conversation because it would be so obvious that the risks outweigh the benefits. And I see this drug really in that light, where you've got a drug with very modest clinical improvement, impact, a high risk that really can't be mitigated regardless of the REMS. So that risk-benefit ratio really doesn't weigh positive, and I don't see any way to modify a REMS to change that balance. Thank you.

DR. SUAREZ-ALMAZOR: Mr. O'Brien?

MR. O'BRIEN: Yes. Joe O'Brien, National Scoliosis Foundation. I voted no. I echo the sentiments of the previous voters and my colleagues. And I would say, echoing myself actually, that I recognize the need for this drug and actually weigh out the risks-benefits of looking at the potential of a total joint replacement and how that compares to the opposite in terms of my potential for bleeding, my potential for death and addiction, et cetera. I think that that outcome, when I weigh it, it is less.

However, as I indicated, in previous drugs when we were looking at them, as it turns out, the side effect actually ended up becoming the major issue. And I am concerned that in this particular drug, the side effect, while it may seem small to some people, may in fact become the -- we just don't know enough whether or not patients will be dealing with a side effect, and in fact becomes the primary issue with multi-joint destruction later on.

I think until such time as we do that -- and a REMS can't approach that. And I think that's part of the additional data that we need, is a better understanding of the mechanism of what the RPOA is as it relates to tanezumab.

DR. SUAREZ-ALMAZOR: Dr. Habel?

DR. HABEL: Yes. This is Laurel Habel. I also voted no. The reason's stated by others. In addition to the additional data that people have suggested would be good to have, I think it would be also helpful to have more patient preference data that incorporates the risk to healthy joints

and that also doesn't have the forced-choice answers.

I would also like to have some more information on when patients are on this drug and their pain is improved, but it's not sufficiently managed, what are their options for managing their pain, and what would be the safe options for doing that. That's all.

DR. SUAREZ-ALMAZOR: Dr. Katz?

DR. KATZ: Lee Katz, Yale University, School of Medicine in New Haven, Connecticut. I voted no. For me, one of the basic principles of medicine is first do no harm. And although I appreciated the sponsor's presentation and the public's comments from yesterday, I'm concerned about the long-term side effect of the sponsor's drug.

Although the knee and the hip are a target site, the systemic effects of the drug have not been adequately explored. For example, imaging of the shoulder or shoulders was obtained, but the results were not really adequately presented. In addition, there are other non-weight-bearing joints

such as the wrist or the hands, which are a very common site for osteoarthritis. According to multiple graphs, the occurrence of rapidly progressive osteoarthritis appears to progress following the conclusion of the study period, but additional monitoring is required.

Finally, I'm concerned that non-musculoskeletal radiologists may not be adequately trained to monitor the progression of osteoarthritis following the initiation of the sponsor's drug. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Cheng?

DR. CHENG: Thank you. Ed Cheng from the University of Minnesota. I'm sorry to say that I voted no as well. I was hoping that we would see a drug that had a greater benefit, where the benefit would outweigh the risk, and unfortunately I don't think that's the case.

The sponsor, I do believe, is doing as much as they reasonably can, and I don't think we've been able to modify appropriately to the point that we make it acceptable. So while I think another

therapy is sorely needed for these patients, I don't think it's this drug.

DR. SUAREZ-ALMAZOR: Dr. Richards?

DR. RICHARDS: John Richards, the VA Pittsburgh Healthcare System. I also voted no, and I did so being at the VA hospital where I see a lot of elderly patients with comorbidities who have a lot of osteoarthritis.

There certainly is need for another therapeutic option but, unfortunately, I think for the reasons previously stated and lack of longer term data, that may demonstrate whether there's a plateauing effect once this drug is stopped in terms of the rapidly progressive osteoarthritis, really limits me from approving this as written.

I think without that data, it prevents us from rally coming up with a risk mitigation strategy despite, I think, the best efforts of the sponsor.

DR. SUAREZ-ALMAZOR: Dr. Nason?

DR. NASON: This is Martha Nason from the National Institute of Allergy and Infectious

Diseases, NIH. I voted no for many of the reasons that have already been stated. I won't rehash them, except to say that I think the long-term data -- both on the people who are taking it for a longer time but also have stopped it, and seeing what's happened to them -- is really important in order to allow us to look at the risk-benefit balance; although I would have also, similar to my colleagues, have hoped for higher efficacy in order to be a successful balance against some of the risks we have seen already.

DR. SUAREZ-ALMAZOR: Dr. Kulldorff?

DR. KULLDORFF: My name is Martin Kulldorff. I voted no. To have a REMS program that would ensure the benefits of tanezumab would outweigh the risks, one would have to have either or both of two things. Either there needs to be some way to determine who are the ones who are at highest risk for the joint adverse reactions or there has to be a monitoring system that one can pick those up early enough before the damage is done. And neither of those is currently in the REMS program,

so I voted no. Thank you.

DR. SUAREZ-ALMAZOR: This is Maria Suarez-Almazor. I voted no. I think it is counter-intuitive to use a drug for osteoarthritis that actually makes osteoarthritis worse. I think longer term data that models what would be actually used in real-world settings for at least a couple of years is really needed to understand the risk of this drug. And until this data is available, it's going to be very difficult to develop a plan for a REMS that can actually mitigate rather than just bring [indiscernible].

Dr. Calis?

DR. CALIS: This is Karim Calis from the NIH, and I voted no as well. Briefly, I would just say that the risk-benefit equation is heavily tilted toward risk. In this case, we're missing critical information from long-term follow-up of the study participants that can potentially inform risk mitigation strategies.

I don't think it's unreasonable to ask the sponsor to attempt a follow-up study of individuals

who previously participated in the tanezumab clinical trials. Ideally, this should have been done earlier. There certainly was an opportunity following resumption of research, after lifting of the clinical hold.

So I wish that had been done, but I think at this point you asked the question, what additional information, and I think it would not be unreasonable to attempt a follow-up study. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Hovinga?

DR. HOVINGA: This is Collin Hovinga from University of Texas, Austin, I-ACT for Children. I voted no for many of the reasons others commented earlier, but I will emphasize that the risk-benefit of the drug wasn't clearly demonstrated in the data that was presented. I think the inability to document who might be sufficiently at risk for developing the long-term toxicities, as well as ways to better earlier detect it, weren't stated.

I think the other thing -- that was very much challenging, and I appreciate the lack of

feasibility in taking this project forward -- would be to literally look at the longer term safety of the medication in this population, given particularly the low clinical benefit that was demonstrated in the data that was presented. Thank you.

DR. SUAREZ-ALMAZOR: Ms. Johnson?

MS. JOHNSON: Hetlena Johnson, a consumer representative and also a community health advocate and researcher. I voted yes. I voted yes because I also felt that the REMS needed more time. With 60 to 65 percent of many drugs that are introduced, they're not given enough time and enough recognition in terms of finding that solution for patients that are suffering right now.

With the REMS, I felt that the patients were advised of what was going on and that they are getting a benefit. But it cannot be completed. It cannot actually get past the risk without getting enough time, and even more, to be studied. So that's one of the reasons why I voted yes. Although I see some things that could be improved,

I really felt that a yes would improve it. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Nelson?

DR. NELSON: Hi. It's Lewis Nelson from Rutgers New Jersey Medical School in Newark, New Jersey. I voted no. A lot of the reasons that have already been stated certainly factored into that decision. I focused a lot on the REMS program itself.

I think we should know a bit more about how REMS work out in the real world by now from the programs that have been implemented in the past. And I think that the program that's been put forth is a bit too porous and probably not going to be very effective. There are too many unknowns. There's a lot of expense that's going to be unloaded onto patients. There are some questions about whether or not we'll be able to be consistent in detecting and identifying radiographic changes based on some of the technologists- and radiologists-related issues.

I think that REMS work best when the risk is

significant or at least is able to be mitigated sufficiently. And it's not clear to me that identifying a risk -- or, I'm sorry, identifying a problem at this point is going to mitigate that problem. I think that because of that, the REMS is probably going to be ineffective even if it did work; but identify the problem. And I'm not clear at all that it will be able to do that.

So for those reasons really related to the REMS program itself, I voted no. Thank you.

DR. SUAREZ-ALMAZOR: Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I voted no because I feel strongly that anticipated chronic use requires that we have a good idea of the long-term problems with this drug. We need at least to show a leveling and a dropping of adverse events, and we don't have that.

The effect on healthy or near healthy joints is very troubling. As the consumer representative on the Drug Safety and Risk Management Committee, informed patient consent is very important to me. If the choice to the patient was as simple as a

1.1 percent risk of needing a joint replacement or a 2.2 percent risk, then I could buy into it. The patient should determine the risk that he or she is willing to take.

But in this case, it's not that simple. Patient preference information is important, but the charge to the FDA is that the benefits must outweigh the risks. When the risk-benefit ratio is out of balance, the patient in the real world, without the benefit of the depth of information that we have, or the time to study the drug that we've taken, and under the pressure of pain, cannot be expected to be in position to make an informed decision. The risks are just not clear yet.

Importantly, the patient has multiple other options that are equal in efficacy. A new drug with risks must have much better efficacy. And if it isn't understood why this drug is working, I don't know how you're going to mitigate its effect. I don't know how you're going to find risk mitigation components that would prevent or reduce the incidence of joint damage.

One never knows all the risks of medicines when they're first approved. We accept that risk. And it can take years to figure it all out. However, in this case, we know what we don't know, and those questions are significant and life-altering. Thanks.

DR. SUAREZ-ALMAZOR: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted no. I would like to clarify that I agree that there is an unmet need and that we need alternatives, particularly for opioids. I would like to congratulate the sponsor for their research and all the studies that they have conducted in this area; however, I still voted no because I don't think this is the game-changer. Therefore, the marginal benefits do not outweigh the risks, even with the REMS.

I will not repeat what others have said, but in terms of modifying the risk mitigation, maybe proposing that the group of patients is really restricted to those that have contraindications for NSAIDs, then maybe in that group the risk may be

lower than the potential benefits. But we cannot base that decision of identifying the group of patients based on promising benefits when the NSAIDs fail because the clinical trials do not support that this drug is going to work better in terms of reducing pain than NSAIDs. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Griffin?

DR. GRIFFIN: Yes. Hi. This is Marie Griffin from Vanderbilt. I voted no, and I don't think that any modification of the REMS program would really help. I think maybe it would be possible to identify a patient population with a different, more optimistic benefit-risk ratio, and I think the sponsor tried to do that, and so did FDA. But unfortunately, I don't think we know of a population where the benefit-risk ratio is good for this drug. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Horton?

DR. HORTON: Yes. Thanks. Dan Horton, Rutgers University, New Brunswick, New Jersey. I voted no for many similar reasons as others. I agree that the REMS program does not seem adequate

to ensure use by the target population, or to identify patients who are at higher risk for harms, or to prevent serious harms from this agent.

I do worry that if it were approved, even with the REMS proposed in place, that the harms seen in the trial would be magnified in the general population. We would see long-term use, and the data presented offered hints that there could be cumulative harms over time and also lead to use by patients with osteoarthritis who were ineligible for the trials, who might be subject to more or different harms. We'd also see off-label use for people without osteoarthritis. And again, this comes back to the risks seen in potentially normal joints.

So in my opinion, these potential harms outweigh the potential benefits. I agree that long-term follow-up data would be very useful, as would data from the MRIs performed as part of the trial, but not interpreted; though I don't necessarily think that that would be feasible in implementing a REMS strategy. Thank you.

DR. SUAREZ-ALMAZOR: Dr. Pisetsky?

DR. PISETSKY: This is Dr. Pisetsky from Duke. I also voted no for the reasons indicated by others. But also I think we simply don't know enough about targeting this particular molecule. It would be a new target, so there are lots of unknowns in terms of the basic biology.

But the other is this is a biologic, and therefore it has a different duration of action than a potential small molecule, and I don't think that enough is really known about the consequences of prolonged inhibition -- we're talking weeks -- in comparison to other therapies. Other therapies can be dose adjusted, even something like selective joint injection as the discretion about use and whether you should or should not do injection.

There are a lot of options for tailoring the program to the patient: fixed dose; biologic; let alone, mechanism of action. I think there are just so many unknowns at this point, that it would be difficult to develop the REMS strategy

appropriately.

DR. SUAREZ-ALMAZOR: Thank you.

I will briefly summarize the justifications brought by the panel for the vote. Firstly, I would like to say that there was recognition by the panel of the unmet need for treatment of osteoarthritis, so that was clearly recognized. However, overall it was felt that benefit did not outweigh the risk.

There was not enough information on long-term data for both those patients receiving active treatment and also those who discontinued treatment and no data on how to identify patients before irreversible lesions happen. There were concerns on the potential effect on healthy joints, lack of knowledge about the biology of the drug and its effect, and also there were concerns about implementation of a REMS program that only identifies but doesn't mitigate risk.

There were doubts about the effectiveness of this program given the lack of evidence on the long-term use of the drug and also because it was

largely dependent on x-ray evaluation by community radiologists.

Before we adjourn, are there any last comments from the FDA?

DR. ROCA: Hi. This is Dr. Roca. I just would like to thank the entire advisory committee panel for a full discussion with respect to the issue. We certainly do appreciate your thoughts and the time you took to discuss them. Thank you.

Adjournment

DR. SUAREZ-ALMAZOR: We will now adjourn the meeting. Thank you.

(Whereupon, at 12:49 p.m., the meeting was adjourned.)